(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 742 207 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
13.11.1996 Bulletin 1996/46

(21) Application number: **96110252.2**

(22) Date of filing: **22.06.1988**

(51) Int. Cl.[6]: **C07D 211/22**, C07D 211/26, C07D 211/76, C07D 211/34, C07D 207/09, C07D 401/06, C07D 401/12, C07D 405/12, A61K 31/445

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(30) Priority: **22.06.1987 JP 155058/87**

(62) Application number of the earlier application in accordance with Art. 76 EPC: **95104080.7**

(71) Applicant: **Eisai Co., Ltd.**
Tokyo (JP)

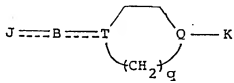
(72) Inventors:
- **Sugimoto, Hachiro**
  Tokyo (JP)
- **Tsuchiya, Yutaka**
  St. Fort Lee, NJ 07024 (US)
- **Higurashi, Kunizou**
  Tokyo (JP)
- **Karibe, Norio**
  Tokyo (JP)
- **Iimura, Youichi**
  Tsukuba-shi, Ibaraki (JP)
- **Sasaki, Atsushi**
  Tsukuba-shi, Ibaraki (JP)
- **Yamanishi, Yoshiharu**
  Ryugasaki-shi, Ibaraki (JP)
- **Ogura, Hiroo**
  Tsuchiura-shi, Ibaraki (JP)
- **Araki, Shin**
  Kitasouma-gun, Ibaraki (JP)
- **Kosasa, Takashi**
  Tsukuba-gun, Ibaraki (JP)
- **Kusota, Atsuhiko**
  Tsuchiura-shi, Ibaraki (JP)
- **Kososa, Michiko**
  Tsukuba-gun, Ibaraki (JP)
- **Yamatsu, Kiyomi**
  Kamakura-shi, Kanagawa (JP)

(74) Representative: **Hansen, Bernd, Dr. Dipl.-Chem. et al**
Hoffmann, Eitle & Partner,
Patentanwälte,
Arabellastrasse 4
81925 München (DE)

Remarks:
This application was filed on 25 - 06 - 1996 as a divisional application to the application mentioned under INID code 62.

(54) 2-(Indan-1-one-2-yl-alkyl)-1-phenylalkyl-piperidines and processes for their preparation

(57) Processes are provided for preparing cyclic amine compounds defined within the formula:



in which J is indanyl, indanonyl, indenyl, indenonyl, indanedionyl, tetralonyl, benzosuberonyl, indanolyl or a divalent group thereof, K is phenyl, an arylalkyl or cynnamyl, B is -(CHR22)r-, R22 being H or methyl, -CO-(CHR22)r-, =(CH-CH=CH)b-, =CH-(CH2)c- or =(CH-CH)d= and the ring including T and Q is piperidine. The compound is useful for the preparation of pharmaceutical compositions and for medicaments effective against senile dementia.

EP 0 742 207 A1

Description

The invention relates to a cyclic amine compound, a therapeutical composition and medical treatment of senile dementia.

(Statement of Prior Arts)

With a rapid increase in the population of aged people, the establishment of the therapy for senile dementia, such as Alzheimer senile dementia, is eagerly desired.

Various attempts have been made to treat the senile dementia with a drug. So far, however, there has been no drug which is very useful for the treatment of these diseases.

Studies on the development of therapeutic agents for these diseases have been made from various aspects. Particularly, since Alzheimer senile dementia is accompanied by the lowering in cholinergic hypofunction, the development of the therapeutic agent from the aspect of an acetylcholine precursor and an acetylcholinesterase inhibitor was proposed and is in fact attempted. Representative examples of the anticholinesterase inhibitor include physostigmine and tetrahydroaminoacridine. However, these drugs have drawbacks such as an unsatisfactory effect and the occurrence of unfavorable side effects. At the present time, there are no decisive therapeutic agents.

In view of the above situation, the present inventors have made extensive and intensive studies on various compounds for many years with a view to developing a drug which has a persistent activity and a high safety.

As a result, the present inventors have found that a piperidine derivative represented by the following general formula (I) can attain the desired object.

Specifically, the compound of the present invention represented by the following general formula (I) has great advantages of having strong and highly selective antiacetylcholinesterase activity, increasing the amount of acetylcholine present in the brain, exhibiting an excellent effect on a model with respect to disturbance of memory, and having a persistent activity and a high safety when compared with physostigmine which is a conventional popular drug in the art, which renders the compound of the present invention very valuable.

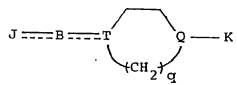
The compound of the present invention was found based on the acetylcholinesterase inhibitory action and, therefore, is effective for treatment and prevention of various diseases which are thought to be derived from the deficiency of acetylcholine as a neurotransmitter in vivo.

Examples of such diseases include various kinds of dementia including Alzheimer senile dementia and further include Huntington's chorea, Pick's disease, and ataxia.

Therefore, the objects of the present invention are to provide a novel piperidine derivative effective as a pharmaceutical, particularly for treatment and prevention of central nervous system diseases, to provide a process for preparing the same, and to provide a pharmaceutical comprising the same as an effective ingredient.

(Summary of the Invention)

The invention provides a cyclic amine compound having the following formula (XXV) and a pharmacologically acceptable salt thereof:



(XXV)

in which J is

(a) a group, substituted or unsubstituted, selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl may have a substituent(s), selected from the group consisting of (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl and (9) C_6H_5-CO-CH(CH_3)-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl or

(e) a group of R^{21}-CH=CH- in which R^{21} is hydrogen or a lower alkoxycarbonyl;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, R^4 being hydrogen, a lower alkyl, an acyl, a lower alkylsul-

fonyl, phenyl, a substituted phenyl, benzyl or a substituted benzyl, -CO-NR^5-$(CHR^{22})_r$-, R^5 being hydrogen, a lower alkyl or phenyl, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, -CH_2-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-CO-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, r being zero or an integer of 1 to 10, R22 being hydrogen or methyl so that one alkylene group may have no methyl branch or one or more methyl branch, =(CH-CH=CH)b-, b being an integer of 1 to 3, =CH-$(CH_2)_c$-, c being zero or an integer of 1 to 9, =(CH-CH)$_d$=, d being zero or an integer of 1 to 5; -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -CH(CH_3)-CO-NH-CH_2-, -CH=CH-CO-NH-$(CH_2)_2$-, -NH-, =O-, -S-, a dialkylaminoalkylcarbonyl or a lower alkoxycarbonyl;

T is nitrogen or carbon;

Q is nitrogen, carbon or $>N\rightarrow O$; and

q is an integer of 1 to 3;

K is hydrogen, phenyl, a substituted phenyl, an arylalkyl in which the phenyl may have a substituent, cynamyl, a lower alkyl, pyridylmethyl, a cycloalkylalkyl, adamantanemethyl, furylmethyl, a cycloalkyl, a lower alkoxycarbonyl or an acyl; and

---- shows a single bond or a double bond.

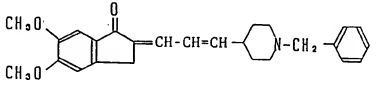
In the compounds having the formula (XXV), it is preferable that J is (a) or (b). In the definition (b), monovalent groups of (2), (3) and (5) and divalent groups of (2) are preferable. In the definition of B, -(CHR22)r-, =(CH-CH=CH)b-, =CH-(CH2)c- and =(CH-CH)d= are preferable. These preferable groups of (B) may be connected with (b) of J, in particular (2) of (b).

It is preferable in the formula (XXV) that Q is nitrogen, T is carbon and n is 1 or 3; and Q is carbon, T is nitrogen and n is 2. It is most preferable that Q is nitrogen, T is carbon and n is 2.

It is preferable that K is a phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

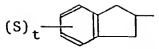
Preferable compounds of the invention include:

1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine,
1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-methylenedioxy-1-indanon)-2-yl)methylpiperidine,
1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-(m-florobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine,
1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine and
1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine, having the below shown formula, shown in Example 224.

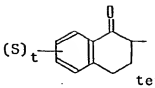


In addition, the invention provides a therapeutical composition which comprises a pharmacologically effective amount of the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier and then a method for preventing and treating a disease due to the acetylcholinesterase activity by administering to a human patient the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof.

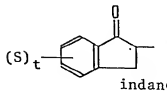
The preferable compound has the above shown formula in which J is (b). The group (b) includes nine groups having the respective formulae shown below. S is hydrogen or a substituent such as a lower alkyl having 1 to 6 carbon atoms and a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferable. t is an integer of 1 to 4. The phenyl is most preferred to have 1 to 3 methoxy groups thereon. $(S)_t$ may form methylene dioxy group or ethylene dioxy group on two adjacent carbon atoms of the phenyl group.



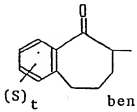
indanyl



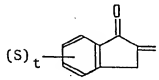
tetranoyl



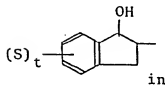
indanonyl



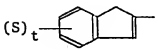
benzosuberonyl



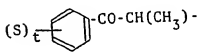
indanolidenyl

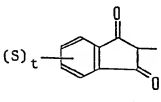


indanoyl

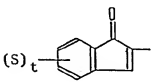


indenyl





indanedionyl



indenonyl

A preferable definition of B includes -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, =(CH-CH=CH)$_b$-, =CH-$(CH_2)_c$- and =$(CH\text{-}CH)_d$=. The group of -$(CHR^{22})_r$- in which R^{22} is hydrogen and r is an integer of 1 to 3 and then the group of =CH-$(CH_2)_c$-are most preferable.

In the above defined cyclic amine compound of the invention, it is preferable that J in the formula is (b) the monovalent or divalent group. In the definition (b), indanonyl, indanedionyl and indenyl are most preferable, optionally having a substituent(s) on the phenyl.

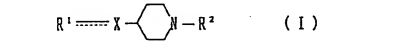
In the definition B, -$(CHR^{22})_r$- and =CH-$(CH_2)_c$-are preferable.

In the ring including T and Q, it may be a 5-, 6- or 7-membered ring. It is preferable that Q is nitrogen, T is carbon or nitrogen and n is 2; Q is nitrogen, T is carbon and n is 1 or 3; and Q is carbon, T is nitrogen and n is 2.

In the definition K, phenyl, an arylalkyl and cynnamyl are preferable, optinally having a substituent(s) on the phenyl.

The invention will be explained in detail in view of the piperidine compounds which fall within the scope of the abode defined cyclic amine compound. The explanation applies to the entire invention of the cyclic amine compound.

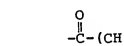
The piperidine compound is defined by the formula (I):



(I)

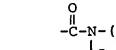
wherein R^1 is the following substituted or unsubstituted group: ① a phenyl group, ② a pyridyl group, ③ a pyrazyl group, ④ a quinolyl group, ⑤ an indanyl group, ⑥ a cyclohexyl group, ⑦ a quinoxalyl group, or ⑧ a furyl group; a monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl ring; a monovalent group derived from a cyclic amide compound; a lower alkyl group or a group represented by the formula R^3-CH=C- (wherein R^3 is a hydrogen atom or a lower alkoxycarbonyl group),

X is a group represented by the formula $-(CH_2)_n-$, a group represented by the formula

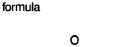


a group represented by the formula

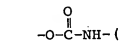
(wherein R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, or a substituted or unsubstituted phenyl or benzyl group), a group represented by the formula



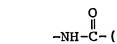
(wherein R^5 is a hydrogen atom, a lower alkyl group, or a phenyl group), a group represented by the formula -CH=CH-$(CH_2)_n$-, a group represented by the formula



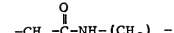
a group represented by the formula



a group represented by the formula -CH=CH-CH=CO-, a group represented by the formula

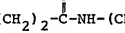


a group represented by the formula



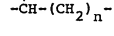
a group represented by the formula

a group represented by the formula



a group represented by the formula

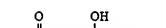
a group represented by the formula



a group represented by the formula

a group represented by the formula

a group represented by the formula



a dialkylaminoalkylcarbonyl group, or a lower alkoxycarbonyl group,

provided that n's in the above definition of X are each independently an integer of 0 to 6,

R^2 is a substituted or unsubstituted phenyl group, a substituted or unsubstituted arylalkyl group, a cinnamyl group, a lower alkyl group, a pyridylmethyl group, a cycloalkylalkyl group, an adamantanemethyl group, or a furoylmethyl group,

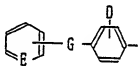
and a symbol, ——, in the above general formula, means a single bond or a double bond.

The term "lower alkyl group" used in the above definition of R^1, R^2, R^4 and R^5 with respect to the compound (I) of the present invention is intended to mean a straight-chain or branched alkyl group having 1 to 6 carbon atoms, and examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopenthyl,

neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, and 1-ethyl-2-methylpropyl groups. Among them, methyl, ethyl, propyl, isopropyl groups etc. are preferable. A methyl group is the most preferable.

Examples of the substituent involved in the expression "the following substituted or unsubstituted group: ① a phenyl group, ② a pyridyl group, ③ a pyrazyl group, ④ a quinolyl group, ⑤ an indanyl group, ⑥ a cyclohexyl group, ⑦ a quinoxalyl group, or ⑧ a furyl group" in the definition of R^1 include lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy group corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms such as chlorine, bromine, and fluorine; a carboxyl group; lower alkoxycarbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group, a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups, such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups including a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy lower alkyl groups such as ethoxymethyl, methoxymethyl, and methoxyethyl groups. The "lower alkyl groups" and "lower alkoxy groups" in the above description of the substituent include all the groups derived from the above-mentioned groups. The substituent may be one to three of them which may be the same or different.

Further, when the substituent is a phenyl group, the following group is within the scope of the substituted phenyl group:



wherein G is a group represented by the formula

a group represented by the formula

a group represented by the formula -O-, a group represented by the formula

a group represented by the formula $-CH_2-O-$, a group represented by the formula $-CH_2-SO_2-$, a group represented by the formula

and a group represented by the formula

and E is a carbon or nitrogen atom.

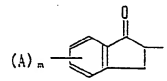
Preferable examples of the substituents for the phenyl group among them include lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxycarbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzoyl and benzylsulfonyl groups. The substituent may be two or more of them which may be the same or different.

Preferable examples of the substituent for the pyridyl group include lower alkyl and amino groups and halogen atoms.

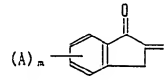
Preferable examples of the substituent for the pyrazyl group include lower alkoxycarbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxycarbonyl groups.

With respect to R^1, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group is preferably a 2-quinolyl or 3-quinolyl group; the quinoxalinyl group is preferable a 2-quinoxalinyl or 3-quinoxalinyl group; and the furyl group is preferably a 2-furyl group.

Specific examples of preferable monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by the following formulae (II) and (III):



(II)

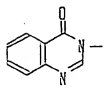


(III)

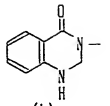
wherein m's are each an integer of 1 to 4 and A's which may be the same or different are each one of the substituents described in the above items ① to ⑧ of the definition of R^1 or a hydrogen atom, preferably a hydrogen atom (i.e. unsubstituted), a lower alkyl group, or a lower alkoxy group, and most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group may be any one having a cyclic amide group in the structural formula thereof and is not limited to the above-described specific examples only. The cyclic amide group may be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocyclic ring is preferably one formed by condensation with a phenyl ring. In this case, the phenyl ring may be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

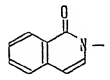
Preferable examples of the monovalent group include the following groups:



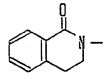
(a)



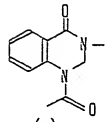
(b)



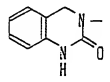
(c)



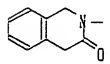
(d)



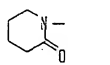
(e)



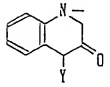
(f)



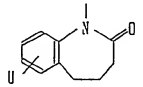
(g)



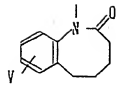
(h)



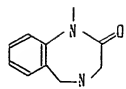
(i)



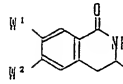
(j)



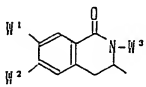
(k)



(l)



(m)



(n)

In the above formulae, Y's in the formulae (i) and (l) are each a hydrogen atom or a lower alkyl group, V in the formula (k) is a hydrogen atom or a lower alkoxy group, W^1 and W^2 in the formulae (m) and (n) are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group and W^3 is a hydrogen atom or a lower alkyl group.

The right-hand ring in each of the formulae (j) and (l) is a seven-membered ring, while the right-hand ring in the formula (k) is an eight-membered ring.

The most preferable examples of the above-defined R^1 include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

The most preferable examples of the above-defined X include a group represented by the formula $-(CH_2)_n-$, a group having an amide group, and groups represented by the above formulae wherein n is 2. Therefore, it is most preferable that any portion of a group represented by the formula $R^{1}\!\!-\!\!-\!\!-\!\!-\!\!-X-$ have a carbonyl or amide group.

The substituents involved in the expressions "a substituted or unsubstituted phenyl group" and "a substituted or unsubstituted arylalkyl group" in the above definition of R^2 are the same as those described in the above items ① to ⑧ in the above definition of R^1.

The term "arylalkyl group" is intended to mean an unsubstituted benzyl or phenethyl group, etc.

Specific-examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

Preferable examples of R^2 include benzyl and phenethyl groups. The symbol $\overset{\frown}{---}$ means either a single or a double bond. This bond is a double bond only when R^1 is the above-described divalent group (III) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

In the present invention, the term "pharmacologically acceptable salt" include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide, and phosphate, and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate, and toluenesulfonate. Further, when a certain kind of substituent is selected, the compound of the present invention may form, e.g., alkali metal salts such as a sodium or potassium salt, alkaline earth metal salts such as a calcium or magnesium salt, organic amine salts such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, or N,N'-dibenzylethylenediamine.

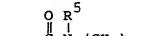
Moreover, the compounds of the present invention may have an asymmetric carbon atom depending upon the kind of the substituent and, therefore, have stereoisomers. They are, of course, within the scope of the present invention.

One specific example thereof will now be described. When R^1 has an indanone skeleton, the compound of the present invention has an asymmetric carbon atom and, therefore, may have stereoisomers, optical isomers, diastereomers, etc. All of these isomers are within the scope of the present invention.

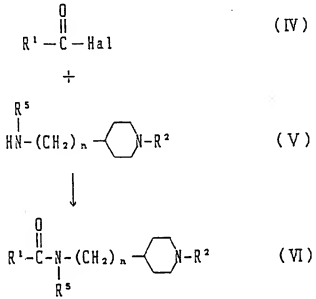
The compound of the present invention may be prepared by various processes. Representative processes for preparing the compound of the present invention will now be described.

Process A

When X in the general formula (I) is a group represented by the formula



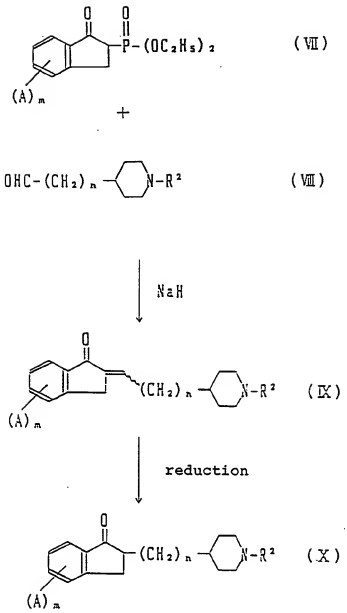
wherein n and R^5 are as defined above, the compound of the present invention can be prepared by the following process:



Specifically, a compound (VI) which is one of the object compounds of the present invention can easily be prepared by reacting an acyl halide represented by the general formula (IV) with a piperidine derivative represented by the general formula (V) in the presence of a demineralizing agent, such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride, or triethylamine, in an organic solvent, such as chloroform, benzene, toluene, dioxane, tetrahydrofuran, or dimethylformamide (DMF), while cooling the reaction mixture or at room temperature or while heating the reaction mixture.

Process B

When R^1 in the general formula (I) is a monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl group and X is a group represented by the formula $-(CH_2)_n-$, wherein n is an integer of 1 to 6, the compound of the present invention can be prepared also by the following process:

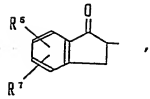


Specifically, a compound (X) which is one of the object compounds can be prepared by reacting a substituted 1-indanon-2-ylphosphonate represented by the general formula (VII) with an aldehyde compound represented by the formula (VIII) (i.e., Wittig reaction) to prepare a compound (IX) which is one of the object compounds and then catalytically reducing said compound (IX).

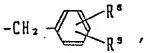
Examples of the catalyst used in the Wittig reaction include sodium methylate (MeONa), sodium ethylate (EtONa), tert-BuOK, and NaH. Examples of the solvent used in this reaction include tetrahydrofuran (THF), dimethylformamide (DMF), ether, nitromethane, and dimethyl sufoxide (DMSO). A reaction temperature ranging from room temperature to about 100°C provides favorable results.

A catalytic reduction in the presence of a catalyst composed of palladium-carbon etc. provides favorable results.

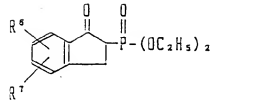
The following scheme specifically shows a process for preparing the compound of the present invention, wherein R^1 is a group represented by the formula



wherein R^6 and R^7 may be the same or different and are each a hydrogen atom, a lower alkyl group, a lower alkylalkoxy group, or a halogen atom among the groups defined by A, X is a group represented by the formula $-(CH_2)_n-$, wherein n is an integer of 1 to 6, R^2 is a group represented by the formula

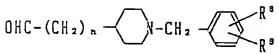


wherein R^8 and R^9 each have the same meaning as that of R^6 and R^7:

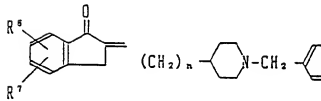


(VI)'

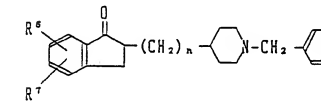
÷



(VII)'



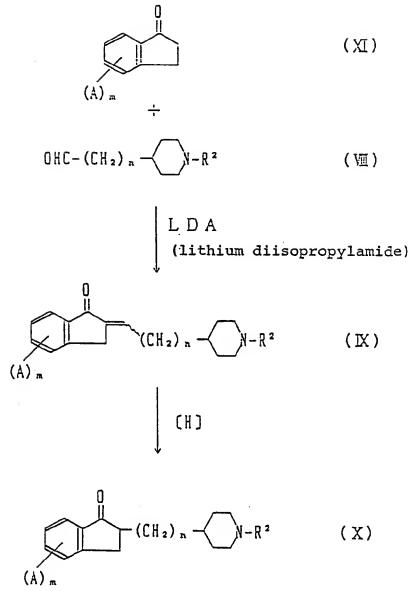
(IX)'



(X)'

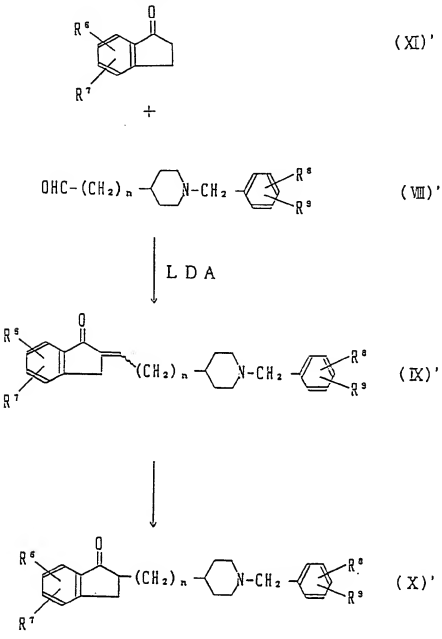
Process C

When R^1 in the general formula (I) is a monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl group and X is a group represented by the formula $-(CH_2)_n-$, wherein n is an integer of 1 to 6, the compound of the present invention can be prepared also by the following process:



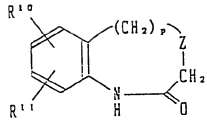
Specifically, for example, diisopropylamine and n-butyllithium/hexane are added to a solvent such as tetrahydrofuran. A substituted 1-indanone represented by the general formula (XI) and hexamethylphosphoric amide are added thereto at a temperature of preferably about -80°C. Then an aldehyde compound represented by the general formula (VIII) are added thereto, followed by a reaction according to an ordinary method. The reaction mixture is subjected to dehydration, thereby preparing a compound (IX). This compound may be catalytically reduced in the same manner as that of the Process B to prepare a compound (X).

A specific example of the Process C will now be described in the same manner as that described in the Process B.



Process D

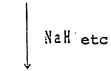
When R^1 is a monovalent group derived from a cyclic amide compound selected from among quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone, the compound of the present invention can be prepared also by the following process:

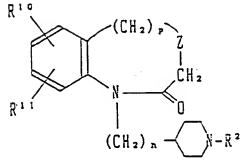


(XII)

÷

(XIII)





(XIV)

wherein R^{10} and R^{11} are each a hydrogen atom, a lower alkyl group, a lower alkoxy group, or a halogen atom, n is an integer of 1 to 6, p is an integer of 1 to 3 and Z is a group represented by the formula $-CH_2-$ or a group represented by the formula

wherein R^{12} is a hydrogen atom or a lower alkyl group.

Specifically, a substituted 1,2,3,4-tetrahydro-5H-1-benzazepin-2-one is allowed to condense with a substituted N-benzyl-4-(2-halogenoethyl)piperidine represented by the general formula (XIII) in a solvent, e.g., dimethylformamide, in the presence of, e.g., sodium hydride, thereby preparing a compound (XIV) which is one of the object compounds.

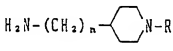
Process E

When R^1 is a group represented by the formula

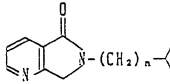
and X is a group represented by the formula $-(CH_2)_n-$, the compound of the present invention can be prepared also by the following process:

(XV)

+



(XVI)

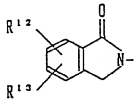


(XVII)

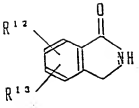
Specifically, 2-hydroxymethylnicotinic acid lactone (XV) is reacted with a substituted N-benzyl(2-aminoethyl)-piperidine represented by the general formula (XVI) by an ordinary method to prepare a compound represented by the general formula (XVII) which is one of the object compounds. The reaction temperature is preferably about 200°C.

Process F

When R^1 in the general formula (I) is a group represented by the formula

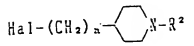


and X is a group represented by the formula $-(CH_2)_n-$, the compound of the presnet invention can be prepared also by the following process:

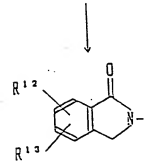


(XVIII)

+



(XIII)

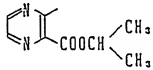


(XIV)

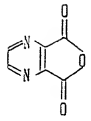
Specifically, a substituted 2,3-dihydroxypyrrolo(3,4-b)benzene represented by the general formula (XVIII) is reacted with a substituted N-benzyl(2-halogenoethyl)piperidine represented by the general formula (XIII) in the presence of, e.g., sodium hydride, in a solvent, such as dimethylformamide, while heating the reaction mirture, thereby preparing a compound (XIV) which is one of the object compounds.

Process G

When R^1 in the general formula (I) is a group represented by the formula

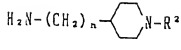


and X is a group represented by the formula -CONH-$(CH_2)_n$-, the compound of the present invention can be prepared also by the following process:

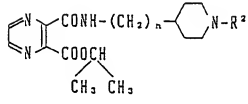


(XX)

+



(XVI)



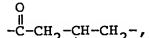
(XXI)

Specifically, 2,3-pyrazylcarboxylic anhydride (XX) is added to, e.g., isopropyl alcohol, followed by reflux. The alcohol is distilled off, and the residue is reacted with a substituted N-benzyl(ω-amino-alkyl) piperidine in a solvent, such as tetrahydrofuran, thereby preparing a compound (XXI) which is one of the object compounds.

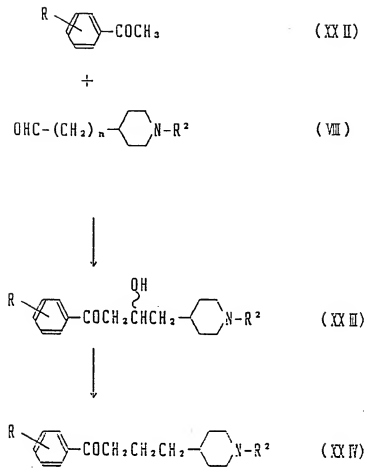
Process H

When R^1 in the general formula (I) is an unsubstituted or substituted phenyl group and X is a group represented by the formula

or a group represented by the formula



the compound of the present invention can be prepared also by the following process:

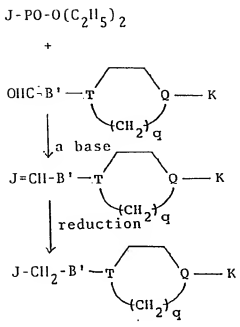


Specifically, diisopropylamine and n-butyllithium/hexane are added to a solvent such as tetrahydrofuran. In the presence of this mixture, an acetophenone represented by the general formula (XXII) is allowed to condense with a substituted N-benzyl (ω-formylalkyl)piperidine, thereby preparing a compound (XXIII). This compound is dehydrated in the presence of, e.g., p-toluenesulfonic acid in a solvent, such as toluene, followed by catalytic reduction according to an ordinary method, thereby preparing a compound (XXIV) which is one of the object compounds.

Process I

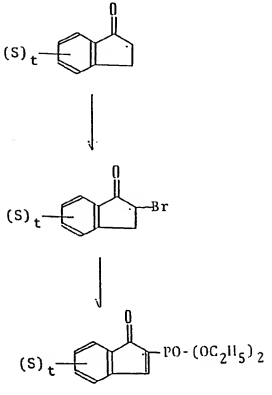
procedure 1

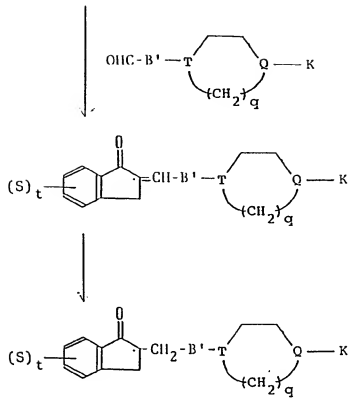
The cyclic amine compound having the formula (XXV) in which J is (1) indanyl, (2) indanonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl or propyophenyl and B is -(CHR22)r-, =(CH-CH=CH)b-, =CH-(CH2)c- or =(CH-CH)d= can be produed by the following procedure. B' is a group where the terminal group containing one carbon atom is excluded from B.



In this procedure, the phosphate is reacted with an aldehyde compound through the Wittig reaction and the product is catalytically reduced. The catalyst to use in the Wittig reaction, includes sodium methylate, sodium ethylate, potassium t-butyrate or sodium hydride. The reaction may be carried out in a solvent such as tetrahydrofurane, dimethylformamide, ether, nitromethane and dimethylsulfoxide at a temperature of the room temperature to 100°c. In the catalytical reduction, it is preferable to use a catalyst such as a catalyst of palladium and carbon, Raney nickel and a catalyst of rhodium and carbon.

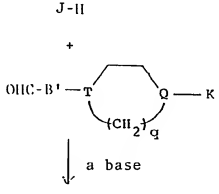
In the above shown procedure, one example in which J is indanonyl goes:

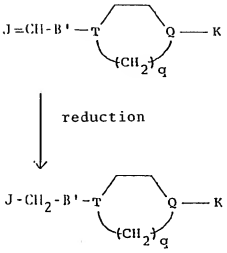




procedure 2

The compound as defined in the procedure 1 can be obtained also in the following way.

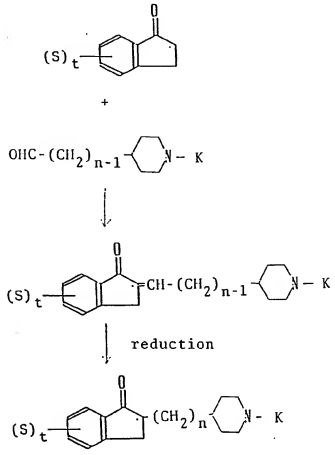




The compound of J-H such as indanone is reacted with an aldehyde by the conventional Aldole condensation to obtain an intended compound. The reaction may be carried but in a solvent such as tetrahydrofurane by first producing lithium di-isopropylamide from di-isopropylamine and a n-butylhexane solution of of lithium, adding thereto a compound of J-H at a temperature of preferably about minus 80°c, then adding the aldehyde thereto, effecting the reaction in the conventional way, heating the production mixture up to the room temperature to conduct dehydration and obtain the enone body of the intended compound. In another manner, the two reactants are dissolved in a solvent such as tetrahydrofurane, a base such as sodium methylate is added to the solution at about 0°c and the reaction is effected at the room temperature.

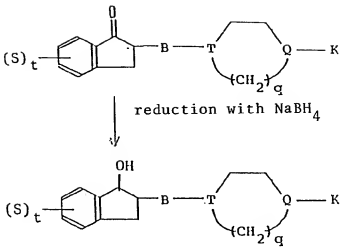
The enone body obtained this way can be reduced to obtain the intended compound.

One example in which J is indanonyl, B is -(CH2)r-and T is carbon, Q is nitrogen and q is 2 goes:



Process J

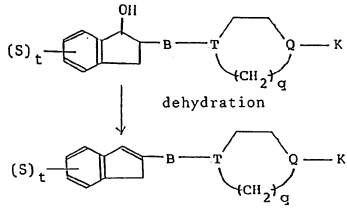
The compound having indanol is produced by the following procedure. This procedure applies to the compound having indanol having a substituent(s) on the phenyl group.



The reduction is effected with sodium boron hydride at 0°c to the room temperature in a solvent such as methanol.

Process K

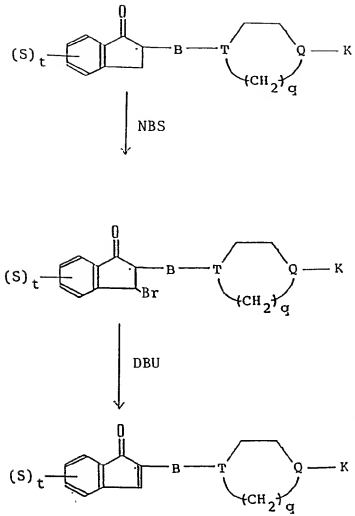
The compound having indenyl is produced by the following procedure. This procedure applies to the compound having indenyl having a substituent(s) on the phenyl.



The dehydration is effected conventionally, for example, with hydrochloric acid.

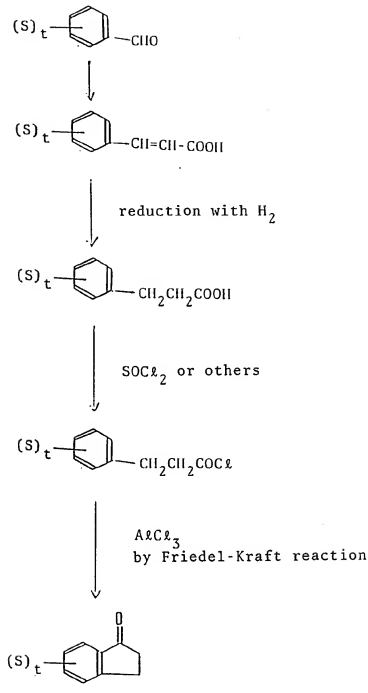
Process L

The compound having indenonyl is produced by the following procedure. This procedure applies to the compound having indenonyl having a substituent(s) on the phenyl.

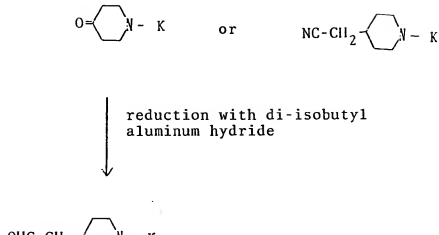


The above shown starting compound having indanone is heated for reflux in a solvent such as carbon tetrachloride in the presence of N-bromosuccinic imide (NBS) and benzoyl peroxide to obtain its bromide and the bromide is heated for reflux in a solvent such as tetrahydrofurane with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) to conduct the beta-elimination and obtain the indenone compound. The bromide may be replaced by another halogenated compound.

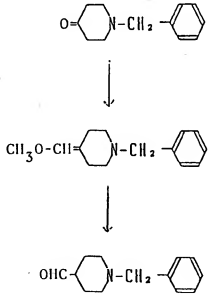
The indanone compound, as used in the above shown processes I, J, K and L, is available in the commmertial market and is produced by the following procedures.


(S)t
CHO
(S)t
CH=CH-COOH
reduction with H2
(S)t
CH2CH2COOH
SOCℓ2 or others
(S)t
CH2CH2COCℓ
AℓCℓ3
by Friedel-Kraft reaction
O
(S)t

The aldenyde compound used above is produced by the following procedures.

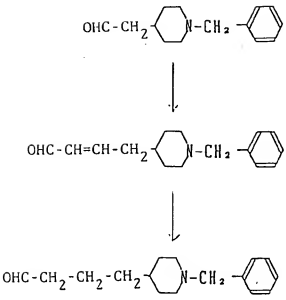


The above shown starting compound is converted to its aldehyde and the aldehyde is bused for the Wittig reaction to increase the carbon number contained therein. The Wittig reaction is effected repeatedly or combined with another kind of the Wittig reaction. This is obvious to a man skilled in the art. The Wittig agent includes methoxymethylenetriphenylphosphorane to add one carbon atom and formylmethylenetriphenylphosphorane to add two carbon atoms. Methoxymethylenetriphenylphosphorane is obtained by the reaction between methoxymethylenetriphenylphosphonium chloride and n-butyl lithium in ether or tetrahydrofurane. Then a ketone compound or an aldehyde compound is added to the product mixture to obtain its methoxyvinyl compound and the resulting mixture is treated with an acid to obtain a corresponding aldehyde. One example goes:



When formylmethylenetriphenylphosphorane is used, a solution of a starting ketone or aldehyde in ether, tetrahydrofurane or bezene is mixed with this Wittig agent and the mixture is heated for reflux to obtain an intended compound.

The obtained unsaturated aldehyde compound may be converted to its saturated compound by the catalytic reduction using a catalyst of palladium and carbon, Raney nickel or a catalyst of rhodium and carbon. One example goes:



The compounds thus prepared and acid addition salts thereof represented by the general formula (I) are useful for treatment of various kinds of senile dementia, in particular senile dementia of the Alzheimer type.

The invention will be described in view of its therapeutical usefulness together with pharmacologically experimental data.

Experimental Example 1

In vitro acetylcholinesterase inhibitory action

A mouse brain homogenate was used as an acetylcholinesterase source and the esterase activity thereof was determined according to the method of Ellman et al.

Ellman, G.L., Courtney, K.D., Andres, V., and Featherstone, R.M., (1961) Biochem. Pharmacol., 7, 88-95.

Acetylthiocholine as a substrate, a sample to detect and DTNB were added to the mouse brain homogenate, followed by incubation. The amount of a yellow substance formed by the reaction between the thiocholine and DTNB was determined in the absorbance at 412 nm in terms of the acetylcholinesterase activity.

The acetylcholinesterase inhibitory activity of the sample was expressed in terms of inhibitory concentration 50% (IC_{50}).

The results are shown in Table 1.

Table 1

Compound	AChE inhibitory activity IC_{50} (μM)	Compound	AChE inhibitory activity IC_{50} (μM)
1	0.23	31	0.025
4	0.0053	33	0.030
5	0.10	45	0.36
6	0.017	48	0.019
8	0.013	52	0.80
9	0.051	54	1.0
10	0.009	56	0.017
11	0.063	62	0.0075
12	0.040	65	0.0016
13	0.026	67	0.10
14	0.038	70	0.28
15	0.094	72	0.020
17	0.052	89	0.018
18	0.68	90	0.035
19	0.064	95	0.085
20	0.54	101	0.11
21	50	120	0.19
23	0.072	124	2.8
24	1.1	176	0.004
26	24		
27	0.41		
29	0.15		

Experimental Example 2

Ex vivo acetylcholinesterase inhibitory action

A sample to detect was orally administered to rats. After one hour of the administration, the cerebral hemispheres were dissected and homogenized, followed by the determination of the acetylcholinesterase activity. The group of rats treated with physiological saline was used as the control. Inhibition of AChE by samples ex vivo was expressed in terms of inhibition percent of the control value. Results are shown in Table 2.

Experimental Example 3

Action on passive avoidance learning impairment induced by scopolamine

See Z.Bokolanecky & Jarvik:Int.J.Neuropharmacol, 6, 217-222(1967).

Male Wister rats were used as the test animal and a step-through light and dark box was used as an apparatus. A sample to detect was orally administered one hour before the training and the rats were treated with 0.5 mg/kg (i.p.) of scopolamine 30 min. before the training. In a training experiment, the animal was placed into a light room and, just after

the animal had entered into a dark room, a guillotine door was closed, followed by delivery of an electric shock from the gid of the floor. After six hours, the animal was again placed into a light room for a retention experiment, and the time taken for the animal to enter the dark room was measured for evaluation of the effect of the sample.

The difference in the response time between the physiological saline administration group and the scopolamine administration group was taken as 100%, and the effect of the sample was expressed in terms of the percentage antagonism by the sample (Reverse %).

The results are shown in Table 3.

Table 2

Compd. No.	Dose (mg/kg)	AChE inhibitory action (%)
Saline		0
4	1	5 *
	3	17 **
	10	36 **
	30	47 **
15	10	5
	30	14 **
	100	18 **

Table 3

Compd. No.	Dose (mg/kg)	Reverse %
4	0.125	55
	0.25	36
13	0.25	39
	0.5	27
15	1.0	51
	2.0	30
19	0. 5	37
	1.0	39
69	0.5	22
	1.0	38

The number of animals per dose was 10 to 17.

NE: non-effective

The above-described pharmacological experiments revealed that the compound of the present invention had a potent acetylcholinesterase inhibitory action.

Among the compounds (I) of the present invention, the compound wherein R^1 is a group (II) or (III) derived from an indanone having an unsubstituted or substituted phenyl ring is preferable, and the compound wherein R^1 is a group represented by the general formula (II) are the most preferable. Specifically, particularly a compound wherein R^1 is a group derived from an indanone having an unsubstituted or substituted phenyl ring has characteristics such as remarkable difference from the conventional acetylcholinesterase inhibitor in the structure, advantages with respect to the manufacture of pharmaceutical preparations by virtue of the potent acetylcholinesterase inhibitory action, large width

between the main and the side effects, persistent activity, high water solubility, excellent stability, advantage in formulating into preparations, high bioavailability and excellent penetration into the brain.

Therefore, the objects of the present invention are to provide a novel compound effective for various kinds of dementia and the sequelae of cerebrovascular diseases, to provide a process for preparing the same, and to provide a novel pharmaceutical comprising the same as an effective ingredient.

Representative compounds of the present invention (Compd. Nos. 4, 13, 15, 19, and 69 in the above Table 3) were applied to toxicity tests on rats. As a result, all the compounds exhibited a toxicity of 100 mg/kg or more, i.e., exhibited no serious toxicity.

The compound of the present invention is effective for treatment, prevention, remission, improvement, etc. of various kinds of senile dementia, particularly senile dementia of the Alzheimer type; cerebrovascular diseases accompanying cerebral apoplexy, e.g. cerebral hemorrhage or cerebral infarcts, cerebral arteriosclerosis, head injury, etc.; and aprosexia, disturbance of speech, hypobulia, emotional changes, recent memory disturbance, hallucinatory-paranoid syndrome, behavioral changes, etc. accompanying encephalitis, cerebral palsy, etc.

Further, the compound of the present invention has a strong and highly selective anticholinesterase action, which renders the compound of the present invention useful also as a pharmaceutical based on this kind of action.

Specifically, the compound of the present invention is effective for, for example, Huntington's chorea, Pick's disease and delayed ataxia or tardive dyskiaesia other than senile dementia of the Alzheimer type.

When the compound of the present invention is used as a pharmaceutical for these diseases, it may be orally or parenterally administered. In general, it is parenterally administered in the form of injections, such as intravenous, subcutaneous, and intramuscular injections, suppositories, or sublingual tablets. The does will remarkably vary depending upon the symptom; age, sex, weight, and sensitivity of patients; method of administration; time and intervals of administration and properties, dispensing, and kind of pharmaceutical preparations; kind of effective ingredients, etc., so that there is no particular limitation with respect to the dose. Normally the compound may be administered in a dose of about 0.1 to 300 mg, preferably 1 to 100 mg, per day per adult, ordinarily in one to four portions.

Pharmaceutical preparations in the dosage form of, e.g., injections, suppositories, sublingual tablets, tablets, and capsules are prepared according to a method which is commonly accepted in the art.

In preparing injections, the effective ingredient is blended, if necessary, with a pH modifier, a buffer, a suspending agent, a solubilizing agent, a stabilizer, a tonicity agent, a preservative, etc., followed by preparation of an intravenous, subcutaneous, or intramuscular injection according to an ordinary method. In this case, if necessary, it is possible to lyophilize these preparations according to an ordinary method.

Examples of the suspending agents include methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, and polyoxyethylene sorbitan monolaurate.

Examples of the solubilizing agent include polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, and an ethyl ester of castor oil fatty acid.

Examples of the stabilizer include sodium sulfite, sodium metasulfite, and ether, and examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, and chlorocresol.

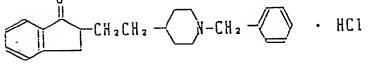
[Examples]

The present invention will now be described in more detail with reference to the following Examples. It is needless to say that the technical scope of the invention of the present invention is not limited to these Examples only.

In the following examples, all of the NMR values are those of the compounds measured in free form.

Example 1

1-Benzyl-4-[2-[(1-indanon)-2-yl]ethylpiperidine hydrochloride



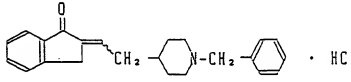
0.37 g of 1-benzyl-4-[2-[(1-indanon)-2-yl]]ethylpiperidine was dissolved in 10 ml of methanol, followed by addition of 0.1 g of 5% rhodium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 24 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride : methanol = 200 : 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.33 g (yield: 80%) of the title compound having the following properties:

- m.p. (°C): 224-225°C

• elementary analysis: $C_{23}H_{27}NO \cdot HCl$			
	C	H	N
calculated (%)	74.68	7.63	3.79
found (%)	74.66	7.65	3.77

Example 2

1-Benzyl-4-[2-[(1-indanon)-2-ylidenyl]]ethylpiperidine hydrochloride

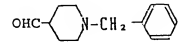


0.32 g of 60% sodium hydride was washed with hexane, and 10 mℓ of THF was added thereto. A solution of 2.12 g of diethyl 1-indanon-2-ylphosphonate in 30 mℓ of THF was dropwise added thereto at 0°C. The mixture was stirred at room temperature for 30 min and again cooled to 0°C, followed by addition of a solution of 3.43 g of 1-benzyl-4-piperidineacetoaldehyde in 10 mℓ of DMF. The mixture was stirred at room temperature for 2 hr and at 50°C for 2 hr and then refluxed for 2 hr while heating the mixture. Methanol and 20% sulfuric acid were added at 0°C to the reaction mixture. 10 min after the addition, the reaction mixture was made basic with an aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride : methanol = 500 : 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain 0.78 g (yield: 27%) of the title compound. 1.37 of diethyl 1-indanon-2-ylphosphorate was also recovered.

- molecular formula; $C_{23}H_{25}NO \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.10~2.13(7H,m)、2.26 (2H,t)、2.88(2H,bd)、3.48(2H,s)、6.72 ~7.07(2H,m)、7.30(5H,s)、7.10~8.00 (5H,m)

Example 3

1-benzyl-4-piperidine-carboaidehyde having the formula:



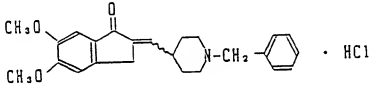
was prepared in the following way.

26 grams of methoxymethylene-triphenylphosphonium chloride was suspended in 200 ml of anhydrous ether. 1.6M solution in hexane of n-butyl lithium was added dropwise to the suspension at the room temperature. The mixture was stirred at the room temperature for 30 minutes and cooled down to 0°c. Then 30 ml of a solution in anhydrous ether of 14.35 g of 1-benzyl-4-piperidone was added to the mixture. It was stirred at the room temperature for 3 hours and filtrated to remove out the insoluble. The filtrate liquid was concentrated at a reduced pressure. The obtained concentrate was dissolved in ether and extracted with 1N hydrochloric acid. An aqueous solution of sodium hydroxide was added to the extract to have pH value of 12. The resultant was extracted with methylene chloride. The extract was dried with magnesium sulfate and concentrated at a reduced pressure. The residue was purified with a column filled with silica gel to obtain 5.50 g of an oil with a yield of 33 percent.

The oil was incorporated into 40 ml of methanol and 40 ml of 1N hydrochloric acid was added to the solution. It was heated so as to make reflux for 3 hours and then concentrated at a reduced pressure. The residue was dissolved in water. An aqueous solution of sodium hydroxide was added to the solution to have a pH value of 12 and the solution was extracted with methylene chloride. The extract was washed with saturated salt solution and dried with magnesium sulfate. It was further concentrated at a reduced pressure and the residue was purified in a column charged with silica gel. 2.77 g of the intended compound was obtained with a yield of 54 percent. In analysis, its molecular formula was found to be C13H17NO and 1H-NMR ($CDCl_3$)δ, 1.40-2.40(7H,m), 2.78(2H, dt), 3.45(2H,S), 7.20(5H,S), 9.51(1H,d).

The compound may be produced according to the methods shown in (1) Arm. Kim. Zh., 36(9), 614-17 (1983) by R.A. Kuroyan, A.I. Markosyan, G.M. Snkhchyan and S.A. Vartangan and (2) Ind. Chim. Belge, 32, 64-5 (1967) by B. Hermans and P. Van Daele.

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine hydrochloride



This reaction was conducted in an argon atmosphere.

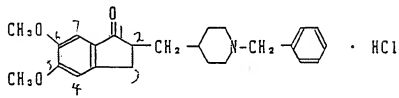
2.05 mℓ of diisopropylamine was added to 10 mℓ of anhydrous THF, followed by addition of 9.12 mℓ of a 1.6 M solution of n-butyllithium in hexane at 0°C. The mixture was stirred at 0°C for 10 min and then cooled to -78°C, and a solution of 2.55 g of 5,6-dimethoxy-1-indanone in 30 mℓ of anhydrous THF and 2.31 mℓ of hexamethyl-phosphoric amide were added thereto. The mixture was stirred at -78°C for 15 min, and a solution of 2.70 g of 1-benzyl-4-piperidine-carboaldehyde in 30 mℓ of anhydrous THF was added thereto. The temperature of the mixture was gradually raised to room temperature, followed by stirring for 2 hr. An aqueous 1% ammonium chloride solution was added thereto, and the organic phase was separated. The water phase was extracted with ethyl acetate, and the organic phases were combined with each other. The combined organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride : methanol = 500 : 1 - 100: 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 3.40 g (yield: 62%) of the title compound having the following properties:

- m.p. (°C): 237-238°C (dec.)

• elementary analysis: $C_{24}H_{27}NO_3$ • HCl			
	C	H	N
calculated (%)	69.64	6.82	3.38
found (%)	69.51	6.78	3.30

Example 4

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride



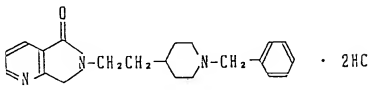
0.4 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine was dissolved in 16 mℓ of THF, followed by addition of 0.04 g of 10% palladium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 6 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride : methanol = 50 : 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.36 g (yield: 82%) of the title compound having the following properties:

• m.p. (°C): 211-212°C (dec.)

• elementary analysis: $C_{24}H_{29}NO_3$ • HCl			
	C	H	N
calculated (%)	69.30	7.27	3.37
found (%)	69.33	7.15	3.22

Example 5

2-[4'-(1'-Benzylpiperidine)ethyl]-2,3-dihydro-1-oxypyrrolo[3,4-b]pyridine dihydrochloride

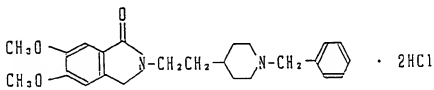


12.6 g of 2-hydroxymethylnicotinic acid lactone and 40 g of 4-(2-aminoethyl)benzylpiperazine were stirred in a sealed tube at 200°C for 7 hr. Thereafter, the reaction mixture was purified by making use of a silica gel column, and a hydrochloride of the purified product was prepared by an ordinary method, thereby preparing 6.37 g of dihydrochloride of the object compound. • m.p. (°C): 143.5-145°C

• elementary analysis: $C_{21}H_{25}N_3O \cdot 2HCl$			
	C	H	N
calculated (%)	61.77	6.66	10.29
found (%)	61.49	6.68	9.98

Example 6

2-[4'-(1'-Benzylpiperidine)ethyl]-2,3-dihydro-5,6-dimethoxyoxypyrrolo[3,4-b]benzene hydrochloride

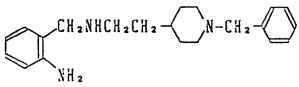


0.5 g of 2,3-dihydro-5,6-dimethoxyoxypyrrolo[3,4-b]benzene was dissolved together with a catalytic amount of potassium iodide in DMF. 0.21 g of sodium hydride (60%) was added to the resulting solution while cooling and stirring the solution. Thereafter, 1 g of 2,3-dihydro-5,6-dimethoxyoxypyrrolo[3,4-b]benzene was added thereto, and the mixture was stirred at 80°C for 4 hr. After the completion of the stirring, H_2O was added thereto, followed by extraction with chloroform. The chloroform phase was washed with water and dried (over $MgSO_4$). The solvent was distilled off, and the residue was purified with silica gel, thereby preparing an oleaginous object compound. A hydrochloride of the object compound was prepared by an ordinary method, thereby obtaining about 0.2 g of a creamy crystal.

- molecular formula; $C_{24}H_{30}N_2O_3 \cdot 2HCl$
- ^{1}H-NMR($CDCl_3$)δ;
  1.12–3.4(9H,m), 2.72 –3.00(2H,m), 3.48(2H,s), 3.62(2H,t), 3.95(6H,s), 4.26(2H,s), 6.90(1H,s), 7.28(6H,s)

Example 7

4-[N-(o-Aminobenzyl)ethyl]-1-benzylpiperidine



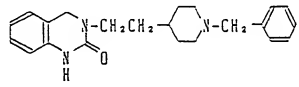
30 g of 2-nitrobenzaldehyde, 21.4 g of 1-benzyl-4-aminoethylpiperidine, and 100 mℓ of methanol were stirred in a nitrogen stream at room temperature for 3 hr. The resulting reaction mixture was cooled with ice, and a solution of 16 g of sodium borohydride in 30 mℓ of MeOH was dropwise added thereto. The reaction was allowed to proceed at room temperature for an additional 1 hr. The reaction mixture was poured into water, extracted with methyl chloride, extracted three times with 150 mℓ of 10% hydrochloric acid, and washed with methylene chloride. Sodium carbonate was added to the water phase to adjust a pH value to 10, followed by extraction with methylene chloride. The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled off in vacuo, thereby preparing 28.4 g of 1-benzyl-4-[N-(o-nitrobenzyl)ethyl]piperidine.

This compound was dissolved in 100 mℓ of methanol and hydrogenated in the presence of 3 g of 10% palladium-carbon (hydrous) at a pressure of 4 kg/cm^2, thereby preparing 25.6 of the title compound.

- molecular formula; $C_{21}H_{29}N_3$
- ^{1}H-NMR($CDCl_3$)δ; 1.0 ~2.1(9H,m)、2.64 (2H,t)、2.90(2H,m)、3.47(2H,s)、6.65 (2H,m)、7.02(2H,m), 7.30(5H,s)

Example 8

3-[2-(1-Benzyl-4-piperidyl)ethyl-2-(1H,3H)-quinazolinone



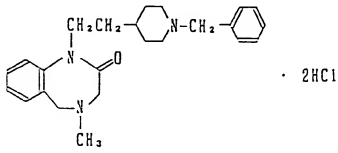
25.6 g of 4-[N-(o-aminobenzyl)ethyl]-1-benzylpiperidine, 15 g of 1,1'-carbonyldiimidazole, and 100 mℓ of methanol were heated under reflux for 12 hr. After the completion of the reaction, the reaction mixture was poured into water, extracted with methylene chloride and dried over magnesium sulfate. The solvent was distilled off in vacuo therefrom.

The residue was purified by silica gel column chromatography (5% MeOH-$CH_2C\ell_2$) and recrystallized twice from ethyl acetate, thereby preparing 3.0 g the title compound.

- molecular formula; $C_{22}H_{27}N_3O$
- ^{1}H-NMR($CDCl_3$)δ; 1.0 ~2.1(9H,m)、2.7 ~3.0(2H,m)、3.2 ~3.6(4H,m)、4.4 (2H,s)、6.5 ~7.4(8H,m)、7.75(1H,s)

Example 9

1-[4'-(1'-Benzylpiperidine)ethyl-1,2,3,4-tetrahydro-4-methyl-5H-[1,4]-benzodiazepin-2-one dihydrochloride



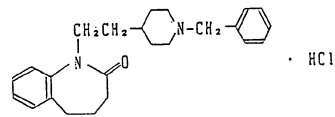
· 2HCl

0.35 g of sodium hydride was suspended in 0.5 mℓ of dimethylformamide (DMF). The suspension was stirred while cooling it with ice, and 0.52 g of 1,2,3,4-tetrahydro-4-methyl-5H-[1,4]-benzodiazepin-2-one dissolved in 3 mℓ of DMF was dropwise added thereto, followed by stirring at room temperature for 30 min. 0.81 g of N-benzyl-4-(2-chloromethyl)piperidine hydrochloride dissolved in 3 mℓ of DMF was dropwise added thereto, and the mixture was stirred at 60 to 70°C for 7 hr. The reaction mixture was poured into ice/water and extracted with methylene chloride. The extract was washed with a saturated saline solution and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography. A hydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 0.17 g of a pale yellow amorphous substance (yield: 13.5%).

- molecular formula; $C_{24}H_{31}N_3O \cdot 2HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.25~2.02(9H,m)、2.52 (3H,s)、2.79~2.95(2H,bd)、3.10(2H, s)、3.48(2H,s)、3.54(2H,s)、3.91(2H, bt)、7.14~7.45(9H,m)

Example 10

1-[4'-(1'-Benzylpiperidine)ethyl]-1,2,3,4-tetrahydro-5H-1-benzazepin-2-one hydrochloride



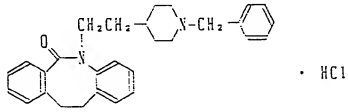
· HCl

0.27 g of sodium hydride was suspended in 0.5 mℓ of dimethylformamide (DMF). The suspension was stirred while cooling it with ice. 0.60 g of 1,2,3,4-tetrahydro-5H-1-benzazepin-2-one dissolved in 4 mℓ of DMF was dropwise added thereto. The mixture was heated at 60°C for 15 min and then cooled with ice. 1.02 g of N-benzyl-4-(2-chloromethyl)piperidine hydrochloride was added thereto, and the mixture was stirred at 60°C for 3.5 hr. The reaction mixture was left to stand for cooling, poured into ice/water, and extracted with methylene chloride. The extract was washed with water and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography. A hydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 1.40 g of the title compound (yield: 94.8%).

- molecular formula; $C_{24}H_{30}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.20~1.92(11H,m)、2.20 ~2.24(4H,bs)、2.60~2.88(4H,m)、3.44 (2H,s)、7.12~7.24(9H,m)

Example 11

N-[4-(1'-Benzylpiperidyl)ethyl]-5,6,11,12-tetrahydrodibenzo[b,f]azocin-6-one hydrochloride



2.24 g of 5,6,11,12-tetrahydrobenzo[b,f]azocin-6-one and 60% sodium hydride were added to 20 mℓ of dimethylformamide. The mixture was stirred at 60°C for 1 hr, and 0.7 g of 1-benzyl-4-chloroethylpiperidine was added thereto, followed by the reaction for an additional 3.5 hr.

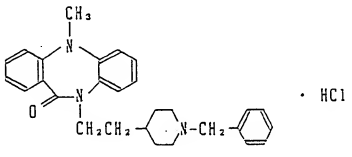
The reaction mixture was poured into 20 mℓ of water, extracted with ethyl acetate, washed with a saturated saline solution, and dried over magnesium sulfate. The solvent was distilled off therefrom in vacuo.

The residue was purified by silica gel column chromatography (5% MeOH in $CH_2C\ell_2$), thereby preparing 0.6 g of the title compound.

- molecular formula; $C_{29}H_{32}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.1 ~2.2(9H,m)、3.7 ~4.1(4H,m)、4.15~4.5(2H,m)、4.46 (2H,s)、6.8 ~7.4(13H,m)

Example 12

10-[4'-(1'-Benzylpiperidine)ethyl]-10,11-dihydro-5-methyl-5H-dibenzo[b,e][1,4]diazepin-11-one hydrochloride

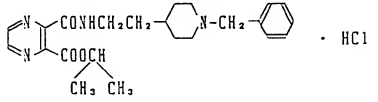


0.25 g of sodium hydride was suspended in dimethylformamide (DMF). The suspension was stirred while cooling it with ice. 0.58 g of 10,11-dihydro-5-methyl-5H-dibenzo[b,e][1,4]diazepin-11-one dissolved in 5 mℓ of DMF was dropwise added thereto. The mixture was stirred at 40 to 50°C for 20 min and then cooled with ice. 0.71 g of 4-(aminoethyl)-1-benzylpiperidine was added thereto, and the mixture was stirred at 45 to 55°C for 6 hr. The reaction mixture was poured into ice/water and extracted with methylene chloride. The organic phase was washed with a saturated saline solution and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography. A hydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 0.78 g of a pale yellow amorphous substance (yield: 65.4%).

- molecular formula; $C_{28}H_{31}N_3O \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.20~1.91(11H,m)、2.60~3.00(2H,bs)、3.22(3H,s)、3.41 (2H,s)、6.87~7.08(3H,m)、7.08(9H,m)、7.64(1H,dd)

Example 13

Isopropyl 3-[[4'-(1'-benzylpiperidine)propionyl]amino]-2-pyrazinecarboxylate hydrochloride

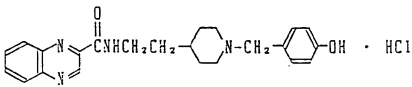


18 g of 2,3-pyrazinecarboxylic anhydride was added to 200 mℓ of isopropyl alcohol, and the mixture was refluxed for 1 hr. Thereafter, the alcohol was distilled off therefrom. The resulting solid was dissolved in THF, and 30.6 g of 4-(2-aminoethyl)benzylpiperidine and 21 g of 1-hydroxybenzotriazole were added thereto. The mixture was stirred while cooling, and 29.7 g of DCC was added to the mixture, followed by a reaction at room temperature overnight. The reaction mixture was filtered and THF was distilled off from the filtrate, followed by addition of methylene chloride. The mixture was washed with an aqueous saturated potassium carbonate solution and then with a saline solution and dried. The solvent was distilled off therefrom. The residue was purified by making use of a silica gel column. The resulting crystal was recrystallized from ether-hexane, thereby preparing 8.81 g of a white crystal of the object compound. A hydrochloride of the compound was prepared by an ordinary method.

• elementary analysis: $C_{23}H_{30}N_4O_3 \cdot HCl \cdot 1/2H_2O$			
	C	H	N
calculated (%)	60.58	7.07	12.29
found (%)	60.54	7.00	12.29

Example 14

N-[4'-(1'-(p-Hydroxybenzyl)piperidine)ethyl]-2-quinoxalinecarboxylic amide hydrochloride



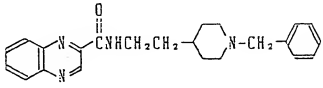
2 g of 2-quinoxalinecarboxylic acid chloride was reacted with 2.52 g of 1-(p-methoxybenzyl)-4-piperidineethylamine in the presence of 2 g of triethylamine in THF at room temperature. The reaction mixture was post-treated by an ordinary method and purified by column chromatography, thereby preparing 2.5 g of N-[4'-(1'-(p-methoxybenzyl)piperidine)ethyl]-2-quinoxalinecarboxylic amide.

This compound was dissolved in 1 g of methylene chloride and reacted with BBr_3 for demethylation. The product was purified by column chromatography, thereby preparing 0.3 g of a product. A hydrochloride of the product was prepared to obtain 0.2 g of a creamy crystal.

- molecular formula; $C_{23}H_{26}N_4O_2 \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.08~1.92(9H,m)、2.84 ~3.18(2H,m)、3.24~3.64(2H,m)、3.52 (2H,s)、6.60(2H,d)、7.05(2H,d)、7.17 (2H,s)、7.64~8.14(4H,m)、9.53(1H,m)

Example 15

N-[4'-(1'-Benzylpiperidyl)ethyl]-2-quinoxalinecarboxylic amide



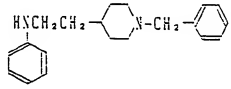
40 g of 2-quinoxaloyl chloride was added to a mixture of 4.6 g of 1-benzyl-4-aminoethylpiperidine, 50 mℓ of pyridine, and 4-dimethylaminopyridine while stirring the mixture at room temperature, followed by a reaction for 3 hr. Thereafter, the reaction mixture was poured into water, extracted with methylene chloride, and dried over anhydrous magnesium sulfate. The solvent was distilled off therefrom.

The residue was purified by silica gel chromatography (5% MeOH-$CH_2C\ell_2$) and recrystallized from ethyl acetate, thereby preparing 3.0 g of the title compound.

- molecular formula; $C_{23}H_{26}N_4O_2 \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.16~2.20(9H,m)、2.76 ~3.04(2H,m)、3.49(2H,s)、3.48~3.68 (2H,t)、7.13~7.40(5H,m)、7.70~8.26 (4H,m)、9.64(1H,s)

Example 16

1-Benzyl-4-(N'-phenylaminoethyl)piperidine



47 g of 4-(N-benzoylpiperidyl) acetate, 8 mℓ of thionyl chloride, and 20 mℓ of benzene were heated under reflux for 2 hr. Thereafter, the solvent was distilled off in vacuo.

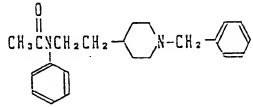
The residue was dissolved in 20 mℓ of THF. The resulting solution was dropwise added to a mixture of 1.86 g of aniline, 10 g of triethylamine, and 30 mℓ of THF while cooling the mixture with ice and, at the same time, stirring the mixture, followed by a reaction at room temperature for about 11 hr. The reaction mixture was poured into water and extracted with methylene chloride. The extract was washed with a saturated saline solution and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel chromatography (5% MeOH in $CH_2C\ell_2$) to prepare 0.9 g of 4-(N-benzoylpiperidyl)acetanilide.

0.9 g of 4-(N-benzoylpiperidyl)acetanilide was dissolved in 10 mℓ of THF. A solution of 0.38 g of lithium aluminum hydride in 30 mℓ of THF was dropwise added to the resulting solution while cooling and stirring the solution. The mixture was heated under reflux for additional 1 hr. After the completion of the reaction, water was added thereto. The resulting precipitate was removed by filtration. The filtrate was extracted with ethyl acetate, washed with a saturated saline solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off in vacuo to prepare 0.7 of 1-benzyl-4-(N'-phenylaminoethyl)piperidine.

- molecular formula; $C_{20}H_{26}N_2$
- ^{1}H-NMR($CDCl_3$)δ; 1.0 ~2.2(9H,m)、2.85 (2H,m)、3.10(2H,t)、3.44(2H,s)、3.7 (1H,bs)、6.4 ~6.8(3H,m)、7.0 ~7.4 (7H,m)

Example 17

N-[4'-(1'-Benzylpiperidyl)ethyl]acetaniiide



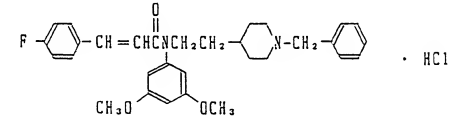
0.4 g of acetyl chloride was dropwise added to a mixture of 0.7 g of 1-benzyl-4-(N'-phenylaminoethyl)piperidine, 2.0 g of triethylamine, and 20 mℓ of THF while cooling the mixture with ice under stirring.

The reaction was allowed to proceed at room temperature for 3 hr, and 20 mℓ of water was added thereto, followed by extraction with methylene chloride. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled off therefrom in vacuo. The residue was purified by column chromatography (5% MeOH in $CH_2C\ell_2$), thereby preparing the title compound.

- molecular formula; $C_{23}H_{28}N_2O$
- ^{1}H-NMR($CDCl_3$)δ; 1.0 ~2.1(12H,m)、2.6 ~3.0(2H,m)、3.39(2H,s)、3.67(2H,t)、6.9 ~7.5(10H,m)

Example 18

N-(3'5'-Dimethoxyphenyl)-N-[4'-(1'-benzylpiperidyl)ethyl]-4-fluorocinnamamide hydrichloride



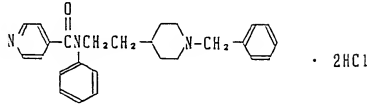
0.51 g of p-fluorocinnamoyl chloride was added to a mixture of 1.0 g of 1-benzyl-4-[N'-(3',5'-dimethoxyphenyl)aminoethyl]piperidine, 2.0 g of triethylamine, and 20 mℓ of THF while cooling the mixture with ice under stirring. The reaction was allowed to proceed at room temperature for 2 hr. Thereafter the reaction mixture was poured into water, extracted with ethyl acetate, washed with a saturated saline solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off therefrom in vacuo.

The residue was purified by silica gel chromatography (5% MeOH in $CH_2C\ell_2$). A hydrochloride of the product was prepared by an ordinary method, thereby obtaining 0.9 g of the title compound.

- molecular formula; $C_{31}H_{35}N_2O_3F \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.1 ~2.1(9H,m)、2.7 ~3.0(2H,bd)、3.51(2H,s)、3.83(8H,m)、6.1 ~6.4(4H,m)、6.9 ~7.8(10H,m)

Example 19

N-[4'-(1'-Benzylpiperidine)ethyl]-N-phenylnicotinamid dihydrochloride

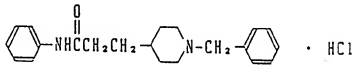


0.70 g of N-[4'-(1'-benzylpiperidine)ethyl]aniline and a catalytic amount of 4-(N,N-dimethylamino)pyridine were dissolved in 30 mℓ of pyridine. The resulting solution was stirred while cooling it with ice. 0.85 g of isonicotinoyl chloride was added thereto, followed by stirring for 3.5 hr. The solvent was distilled off in vacuo. The residue was purified by making use of a silica gel column. A dihydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 0.75 g of a pale yellow amorphous substance (yield: 73.0%).

- molecular formula; $C_{26}H_{29}N_3O \cdot 2HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.13~2.01(9H,m)、2.81 (2H,bd)、3.44(2H,s)、3.88(2H,bt)、6.84~7.26(12H,m)、8.31(2H,d)

Example 20

4-(1-Benzylpiperidine)propananilide hydrochloride



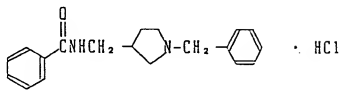
0.5 g of aniline and 1 g of triethylamine were dissolved in THF. 1 g of 4-(1-benzylpiperidine)propionyl chloride was dropwise added to the resulting solution while stirring the solution, followed by a reaction at room temperature for 5 hr. Thereafter the solvent was distilled off and methylene chloride was added to the residue. The resulting solution was washed with water and dried over $MgSO_4$. The solvent was again distilled off and the residue was purified by making use of a silica gel column, thereby preparing the object compound in the form of oleaginous matter. A chloride of this compound was prepared by an ordinary method, thereby obtaining 0.14 g of a white crystal.

- m.p. (°C): 197.5-198°C

• elementary analysis: $C_{21}H_{26}N_2C \cdot HCl$			
	C	H	N
calculated (%)	70.28	7.58	7.81
found (%)	70.50	7.58	7.83

Example 21

N-[3'-(1'-Benzylpyrrolidine)methyl]benzamide hydrochloride

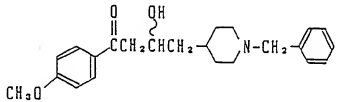


0.74 g of benzyl chloride was reacted with 1 g of 3-(2'-aminomethyl)benzylpyrrolidine in the presence of 1.5 g of triethylamine in THF at room temperature while stirring the reaction system. The reaction mixture was post-treated by an ordinary method and purified by column chromatography, thereby preparing 0.32 g of the object compound. A hydrochloride of the compound was prepared by an ordinary method.

- molecular formula; $C_{19}H_{22}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ;
  1.48~3.08(7H,m)、3.44(2H,d)、3.62(2H,d)、7.04~7.88(10H,m)

Example 22

4-[4'-(N-Benzyl)piperidyl]-3-hydroxy-p-methoxybutyrophenone

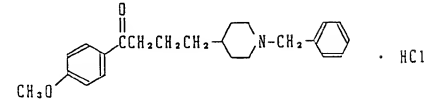


2 mℓ of diisopropylamine was added to 7 mℓ of THF in a nitrogen stream. 7.6 mℓ of a 1.6 M solution of n-butyllithium in hexane was added thereto at 0°C. The mixture was stirred for 10 min and then cooled to -78°C. A solution of 1.65 g of p-methoxyacetophenone in 10 mℓ of THF was added thereto, and the mixture was stirred for 20 min. Further, a solution of 2.4 g of 1-benzyl-4-piperidinecarboaldehyde in 10 mℓ of THF was added thereto, and the mixture was stirred for 10 min. An aqueous 1% ammonium chloride solution was added to the reaction mixture, followed by extraction with methylene chloride. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography (5% MeOH-$CH_2C\ell_2$), thereby preparing 2.0 g of the title compound.

- molecular formula; $C_{23}H_{29}NO_3$
- ^{1}H-NMR($CDCl_3$)δ; 1.0 ~2.2(9H,m)、2.6 ~3.4(5H,m)、3.43(2H,s)、3.81(3H,s)、4.1(1H)、6.83(1H,d)、7.17(5H,s)、7.82(2H,d)

Example 23

4-[4'-N-Benzyl)piperidyl]-p-methoxybutyrophenone hydrochloride

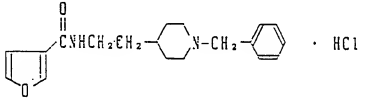


0.54 g of 4-[4'-(N-benzyl)piperidyl]-3-hydroxy-p-methoxybutyrophenone, 0.1 g of p-toluenesulfonic acid, and 30 mℓ of toluene were heated under reflux for 5 hr by making use of a Dean-Stark reflux condenser. After the completion of the reaction, the reaction mixture was poured into an aqueous potassium carbonate solution, extracted with methylene chloride, and dried over anhydrous magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by column chromatography (5% MeOH-CH_2Cl_2) to prepare 0.45 g of 1-benzyl-4-[4-(p-methoxyphenyl)-4-oxobuty[]piperidine. This compound was dissolved in 20 mℓ of MeOH and 40 mg of 10% palladium-carbon (anhydrous) was added thereto to effect hydrogenation at room temperature under atmospheric pressure for 1.5 hr. The insolubles were filtered off, and the solvent was distilled off in vacuo. A hydrochloride of the product was prepared by an ordinary method. The hydrochloride was recrystallized from MeOH-IPE, thereby preparing 0.2 g of the title compound.

- molecular formula; $C_{22}H_{29}NO_2 \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.4 ~2.3(11H,m)、2.4 ~2.7(2H,m)、2.95(2H,t)、3.55(2H,s)、3.87(3H,s)、6.93(2H,d)、7.1 ~7.5(5H,m)、7.94(2H,d)

Example 24

N-[4'-(1'-Benzylpiperidine)ethyl]-3-furancarboxylic amide hydrochloride

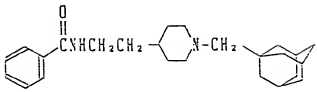


1.64 g of 4-(2-aminoethyl)-1-benzylpiperidine and 2.67 g of potassium carbonate were added to a mixture comprising 40 mℓ of chloroform and 40 mℓ of water. The mixture was stirred for 1 hr while cooling it with ice. The organic phase was separated, washed with a saturated saline solution, and dried over magnesium sulfate. The solvent was distilled off in vacuo and the residue was purified by making use of a silica gel column. A hydrochloride of the product was prepared by an ordinary method, thereby obtaining 1.60 g of the title compound in the form of a pale yellow amorphous substance (yield: 61.1%).

- molecular formula; $C_{19}H_{24}N_2O_2 \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 1.47~2.10(9H,m)、2.81 (2H,bd)、3.25~3.47(4H,m)、5.80(1H, bs)、6.51(1H,dd)、7.15~7.19(6H,m)、7.82(1H,dd)

Example 25

N-[4'-Benzylpiperidine)ethyl]benzamide

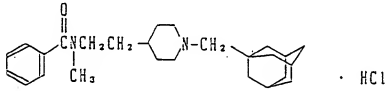


1.47 g of N-(1-adamantanemethyl)-4-(2-aminoethyl)piperidine and 0.73 g of potassium carbonate were added to a mixture comprising 15 mℓ of chloroform and 15 mℓ of water. The mixture was vigorously stirred while cooling it with ice. 0.90 g of benzoyl chloride was added to the mixture, followed by stirring at room temperature overnight. The organic phase was separated, washed with water and a saturated saline solution, and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by making use of a silica gel column. The purified product was recrystallized from benzene-n-hexane, thereby preparing 1.47 g of the title compound in the form of a pale yellow plate crystal (yield: 72.6%).

- molecular formula; $C_{25}H_{36}N_2O$
- ^{1}H-NMR($CDCl_3$)δ; 1.29~2.28(27H,m)、2.72(2H,bs)、3.43(2H,q)、6.01(1H,bs)、7.31~7.43(3H,m)、7.67(1H,dd)

Example 26

N-Methyl-N-[4'-(1'-benzylpiperidine)ethyl]benzamide hydrochloride



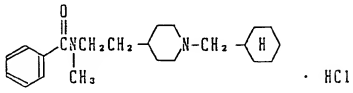
0.18 g of sodium hydride was suspended in 2 mℓ of tetrahydrofuran (THF). The suspension was stirred while cooling it with ice. A solution of 1.45 g of N-[4'-(1'-benzylpiperidine)ethyl]benzamide dissolved in 5 mℓ of THF was dropwise added thereto. The mixture was stirred at room temperature for 1 hr and again cooled with ice. 0.36 mℓ of methyl iodide was added thereto, followed by stirring at room temperature overnight. The reaction mixture was poured into ice/water, extracted with chloroform while conducting salting out, washed with a saturated saline solution, and dried over magnesium sulfate. The solvent was distilled off in vacuo and the residue was purified by silica gel chromatography. Thus there was prepared 0.60 g of yellow oleaginous matter (yield: 47.0%).

The starting material (0.22 g) remaining unmethylated was recovered (recovery: 15.2%). A hydrochloride of the obtained oleaginous matter was prepared bye an ordinary method, thereby obtaining 0.52 g of the title compound in the form of a yellow amorphous substance (yield: 37.6%).

- molecular formula; $C_{26}H_{38}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 0.92~3.60(63H,m)、7.29(5H,s)

Example 27

N-[4'-(1'-Cyclohexylmethylpiperidyl)ethyl]-N-methylbenzamide hydrochloride



0.6 g of N-methyl-N-(4'-piperidylethyl)benzamide, 1.2 g of cyclohexyl bromide, 2.0 g of sodium bicarbonate, and 30 m*l* of methyl ethyl ketone were heated under reflux for 7 hr. After the completion of the reaction, water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel chromatography (5% MeOH-$CH_2C\ell_2$), thereby preparing 0.3 g of the title compound.

- molecular formula; $C_{22}H_{34}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$)δ; 0.8 ~1.1(20H,m)、1.1 ~1.6(4H,m)、1.8 ~2.6(5H,m)、7.4 (5H,s)

Examples 28 to 177

The compounds synthesized in the same manner as that of Examples 1 to 27 are shown in Tables 4 to 8.

Table 4

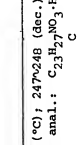
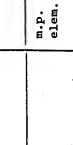
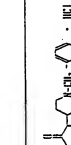
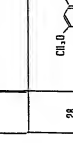
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
28		m.p. (°C); 247~248 (dec.) elem. anal.: $C_{23}H_{27}NO_3 \cdot HCl$ C H N calcd. (%) 68.73 7.02 3.48 found (%) 68.70 6.99 3.55
29		m.p. (°C); 196~197 elem. anal.: $C_{22}H_{25}NO \cdot HCl$ C H N calcd. (%) 74.24 7.36 3.94 found (%) 74.25 7.56 3.80
30		m.p. (°C); 203~204 (dec.) elem. anal.: $C_{23}H_{27}NO_2 \cdot HCl$ C H N calcd. (%) 71.58 7.31 3.63 found (%) 71.58 7.25 3.65
31		^{1}H-NMR($CDCl_3$)δ; 1.10~3.40(14H,m),3.48(2H,s),3.81(3H,s), 3.85(3H,s), 3.85(3H,s), 6.25(1H,bs), 6.42(1H,bs),7.25(5H,s) mol. form.; $C_{24}H_{29}NO_3 \cdot HCl$
32		^{1}H-NMR($CDCl_3$)δ; 1.05~3.40(14H,m), 3.45(2H,s), 3.80(3H,s), 3.85(3H,s), 6.75(2H,ABq), 7.22(5H,s) mol. form.; $C_{24}H_{29}NO_3 \cdot HCl$

Table 4 (cont'd)

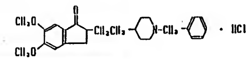
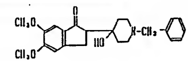
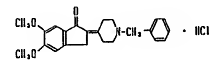
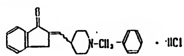
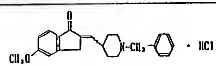
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
33		m.p. (°C); 201∿202 (dec.) elem. anal.: $C_{25}H_{31}NO_3 \cdot HCl$ C H N calcd. (%) 69.83 7.50 3.26 found (%) 69.13 7.42 3.31 $1/5H_2O$ (%) 69.25 7.53 3.23
34		^1H-NMR ($CDCl_3$) δ; 1.10∿3.40(11H,m), 3.50(2H,s), 3.85(3H,s), 3.93(3H,s), 4.25(1H,bs), 6.81(1H,s), 7.07(1H,s), 7.22(5H,s) mol. form.; $C_{23}H_{27}NO_4$
35		m.p. (°C); 225∿226 (dec.) elem. anal.: $C_{23}H_{25}NO_3 \cdot HCl$ C H N calcd. (%) 69.08 6.55 3.50 found (%) 68.78 6.43 3.50
36		m.p. (°C); 169∿170 (dec.) elem. anal.: $C_{22}H_{23}NO \cdot HCl$ C H N calcd. (%) 74.67 6.84 3.96 found (%) 74.42 6.61 3.76
37		m.p. (°C): 120∿122 elem. anal.: $C_{23}H_{25}NO_2 \cdot HCl$ C H N calcd. (%) 71.96 6.83 3.65 found (%) 71.84 6.85 3.46

Table 4 (cont'd)

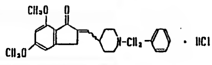
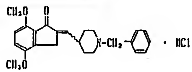
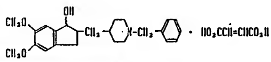
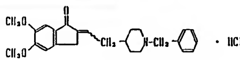
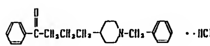
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
38		^{1}H-NMR ($CDCl_3$) δ; 1.40∿2.40 (7H,m), 2.90 (2H,bd), 3.48 (2H,s), 3.51 (2H,bd), 3.82 (3H,s), 3.86 (3H,s), 6.30 (1H,bd), 6.43 (1H,bd), 6.50 (1H,bt), 7.23 (5H,s) mol. form.; $C_{24}H_{27}NO_3 \cdot HCl$
39		^{1}H-NMR ($CDCl_3$) δ; 1.40∿2.50 (7H,m), 2.86 (2H,bd), 3.50 (4H,s), 3.90 (3H,s), 3.94 (3H,s), 6.59 (1H,dt), 6.78 (2H,ABq), 7.22 (5H,s) mol. form.; $C_{24}H_{27}NO_3 \cdot HCl$
40		^{1}H-NMR ($CDCl_3$) δ; 1.14∿2.04 (14H,m), 3.49 (2H,s), 3.81 (6H,s), 4.77 (3H,dd), 6.65 (1H,d), 6.82 (1H,d), 7.23 (5H,s) mol. form.; $C_{24}H_{31}NO_3 \cdot C_4H_4O_4$
41		^{1}H-NMR ($CDCl_3$) δ; 1.10∿2.32 (9H,m), 2.90 (2H,bd), 3.52 (4H,s), 3.89 (3H,s), 3.93 (3H,s), 6.71 (1H,tt), 6.84 (1H,s), 7.20 (1H,s), 7.24 (5H,s) mol. form.; $C_{25}H_{29}NO_3 \cdot HCl$
42		m.p. (°C); 149∿150 elem. anal.: $C_{22}H_{27}NO \cdot HCl$ C / H / N calcd. (%) 73.83 / 7.88 / 3.91 found (%) 71.29 / 8.00 / 3.80 7/10H_2O(%) 71.31 / 8.00 / 3.78

Table 4 (cont'd)

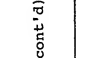
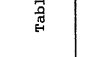
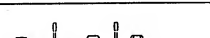
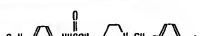
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
43		^{1}H-NMR(CDCl$_3$)δ; 1.80~2.03(13H,m), 2.80(3H,bd), 3.43(2H,s), 4.60(1H,t), 7.28(5H,s), 7.30(5H,s) mol. form.; $C_{22}H_{29}NO\cdot HCl$
44		^{1}H-NMR(CDCl$_3$)δ; 1.10~2.13(7H,m), 2.26(2H,t), 2.88(2H,bd), 3.48(2H,s), 6.72~7.07(2H,m), 7.30(5H,s), 7.10~8.00(5H,m) mol. form.; $C_{22}H_{25}NO\cdot HCl$
45		m.p. (°C); 176~178 elem. anal.: $C_{21}H_{26}N_2O\cdot 2HCl$ C H N calcd. (%) 63.80 7.14 7.09 found (%) 63.13 7.43 6.88 3/10H$_2$O(%) 62.94 7.19 6.99
46		^{1}H-NMR(CDCl$_3$)δ; 1.05~2.15(9H,m), 2.85(2H,bd), 3.02(2H,d), 3.25(1H,bs), 3.47(2H,s), 4.10~4.45(1H,m), 7.21(5H,s), 7.62(2H,dd), 8.70(2H,dd) mol. form.; $C_{21}H_{26}N_2O_2$
47		^{1}H-NMR(CDCl$_3$)δ; 1.10~2.10(7H,m), 2.25(2H,bd), 2.85(2H,bd), 3.45(2H,bs), 6.59~7.10(2H,m), 7.20(5H,s), 7.56(2H,dd), 8.67(2H,dd) mol. form.; $C_{21}H_{24}N_2O\cdot 2HCl$

Table 4 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
48		m.p. (°C); 240~240.7 elem. anal.: $C_{20}H_{25}N_3O \cdot 2HCl$ C H N calcd. (%) 66.75 7.28 11.68 found (%) 66.26 7.42 11.37 $3/20H_2O$(%) 66.25 7.31 11.59
49		^{1}H-NMR($CDCl_3$) δ; 1.80~2.24(9H,m), 2.96(2H,d), 3.64(1H,m), 4.60(1H,m), 7.20~7.58(6H,m), 8.34(2H,d) mol. form.; $C_{19}H_{21}N_3O_2 \cdot HCl$
50		^{1}H-NMR($CDCl_3$) δ; 1.12~2.20(7H,m), 2.34(2H,d), 2.74~3.01(2H,m), 3.50(2H,s), 7.29(2H,s), 7.71(2H,d), 8.20(2H,d)

EP 0 742 207 A1

Table 5

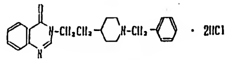
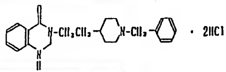
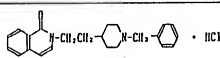
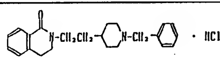
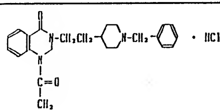
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
51		m.p. (°C); 135∿140 (dec.) elem. anal.: $C_{22}H_{25}N_3O \cdot 2HCl$ C H N calcd. (%) 62.86 6.47 10.00 found (%) 59.22 6.63 9.14 3/2H2O (%) 59.06 6.76 9.39
52		m.p. (°C); 80∿82 (dec.) elem. anal.: $C_{22}H_{27}N_3O \cdot 2HCl$ C H N calcd. (%) 62.56 6.92 9.95 found (%) 60.14 7.313 9.21 1·H2O (%) 60.00 7.09 9.54
53		^1H-NMR($CDCl_3$)δ; 1.1∿2.2(9H,m), 2.7∿3.1(2H,m), 3.50(2H,s) 4.03(2H,t), 6.50(1H,m), 6.9∿7.9(9H,m), 8.47(1H,d) mol. form.; $C_{23}H_{26}N_2O \cdot HCl$
54		^1H-NMR($CDCl_3$)δ; 1.1∿2.2(9H,m), 2.7∿3.1(4H,m), 3.4∿3.7 (6H,m), 7.0∿7.6(8H,m), 8.06(1H,m) mol. form.; $C_{23}H_{28}N_2O \cdot HCl$
55		^1H-NMR($CDCl_3$)δ; 1.10∿2.20(11H,m), 2.27(3H,m), 2.93(2H,bd), 3.48∿3.70(4H,m), 7.27(5H,s), 7.28∿8.12 (4H,m) mol. form.; $C_{24}H_{29}N_3O_2 \cdot HCl$

Table 5 (cont'd)

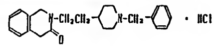
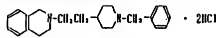
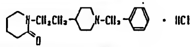
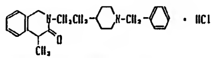
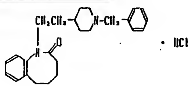
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
56		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.20(9H,m) 2.93(2H,bd), 3.40∿3.65 (6H,m), 4.43(2H,s), 7.00∿7.50(4H,m), 7.31(5H,s) mol. form.; $C_{23}H_{28}N_2O \cdot HCl$
57		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.20(9H,m), 2.22∿2.97(8H,m), 3.45(2H, s), 3.55(2H,s), 6.90∿7.20(4H,m), 7.20(5H,s) mol. form.; $C_{23}H_{30}N_2 \cdot 2HCl$
58		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.16(13H,m), 2.16∿2.50(2H,m), 2.87 (2H,bd), 3.03∿3.43(4H,m), 3.48(2H,s), 7.27(5H,s) mol. form.; $C_{19}H_{20}N_2O \cdot HCl$
59		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.10(9H,m), 1.46(3H,d), 2.87(2H,bd), 3.35∿3.72(3H,m), 3.46(2H,s), 4.40(2H,dd), 7.00∿7.38(4H,m), 7.28(5H,s) mol. form.; $C_{24}H_{30}N_2O \cdot HCl$
60		^{1}H-NMR($CDCl_3$)δ; 1.20∿2.84(2H,m), 3.44(2H,s), 7.14∿7.25 (9H,m) mol. form.; $C_{25}H_{32}N_2O \cdot HCl$

Table 5 (cont'd)

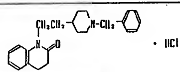
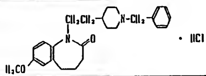
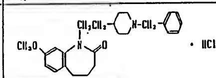
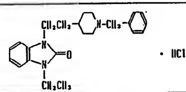
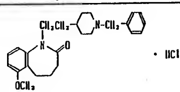
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
61		^{1}H-NMR($CDCl_3$)δ; 1.44∿1.80(15H,m), 2.96(2H,bs), 2.56(2H,s), 7.08∿7.40(9H,m) mol. form.; $C_{23}H_{28}N_2O \cdot HCl$
62		^{1}H-NMR($CDCl_3$)δ; 1.24∿2.50(5H,m), 2.18(2H,bs), 2.54∿2.88 (4H,m), 3.44(2H,s), 3.76(3H,s), 6.64∿6.76 (2H,m), 6.99(1H,d), 7.20(5H,s) mol. form.; $C_{25}H_{32}N_2O_2 \cdot HCl$
63		^{1}H-NMR($CDCl_3$)δ; 1.25∿2.20(15H,m), 2.58(2H,bt), 2.86(2H,bs), 3.48(2H,s), 3.75(3H,s), 6.56∿6.68(2H,m), 7.00(1H,d), 7.21(5H,s) mol. form.; $C_{25}H_{32}N_2O_2 \cdot HCl$
64		^{1}H-NMR($CDCl_3$)δ; 1.38∿2.02(12H,m), 2.96(2H,d), 5.60(2H,s), 4.94(4H,m), 7.08∿7.36(9H,m) mol. form.; $C_{23}H_{29}N_3O \cdot HCl$
65		^{1}H-NMR($CDCl_3$)δ; 1.32∿2.36(15H,m), 2.84∿3.02(2H,m), 3.59(2H,s), 4.09(3H,s), 6.72∿6.88(2H,m), 7.20∿7.44(7H,m) mol. form.; $C_{25}H_{32}N_2O_2 \cdot HCl$

Table 5 (cont'd)

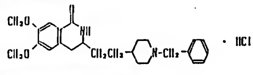
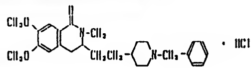
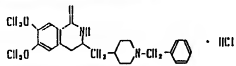
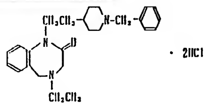
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
66		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.10(11H,m), 2.60∿3.00(4H,m), 3.45 (2H,s), 3.45∿3.80(1H,m), 3.86(6H,s), 6.22 (1H,bs), 6.57(1H,s), 7.20(5H,s), 7.46(1H,s) mol. form.; $C_{25}H_{32}N_2O_3$·HCl
67		^{1}H-NMR($CDCl_3$)δ; 1.08∿2.10(11H,m), 2.50∿2.95(4H,m), 3.01 (3H,s), 3.45(2H,s), 3.45∿3.60(1H,m), 3.85 (6H,s), 6.52(1H,s), 7.10(1H,s), 7.20(5H,s) mol. form.; $C_{26}H_{34}N_2O_3$·HCl
68		^{1}H-NMR($CDCl_3$)δ; 1.02∿2.12(9H,m), 2.50∿3.05(4H,m), 3.43(2H, s), 3.43∿3.85(1H,m), 3.88(6H,s), 6.58(1H, s), 6.50∿6.82(1H,m), 7.20(5H,s), 7.46(1H, s) mol. form.; $C_{24}H_{30}N_2O_3$·HCl
69		^{1}H-NMR($CDCl_3$)δ; 1.17(3H,t), 1.10∿2.15(9H,m), 2.68(2H,q), 2.89(2H,bd), 3.14(2H,s), 3.51(2H,s), 3.55(2H,s), 3.87(2H,bt), 7.07∿7.35(9H,m) mol. form.; $C_{25}H_{33}N_3O$·2HCl

Table 6

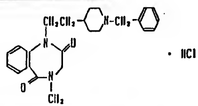
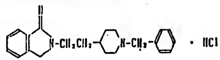
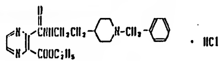
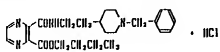
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
70		^{1}H-NMR($CDCl_3$)δ; (in free form) 1.01∿2.40(9H,m), 2.70∿3.30(4H,m), 3.46(3H,s), 3.54(2H,s), 3.90∿4.20(2H,m), 6.90∿8.20(9H,m) mol. form.; $C_{24}H_{29}N_3O_2$·HCl
71		^{1}H-NMR($CDCl_3$)δ; 1.12∿2.12(9H,m), 2.76∿3.00(2H,m), 3.50(2H,s), 3.66(2H,t), 4.36(2H,s), 7.08∿7.92(9H,m)
72		^{1}H-NMR($CDCl_3$)δ; 1.08∿2.16(9H,m), 1.42(3H,t), 2.76∿3.00 (2H,m), 3.32∿3.62(2H,m), 3.50(2H,m), 4.53(q,2H), 7.12∿7.40(5H,m), 7.48∿7.72 (1H,m), 8.58(1H,d), 8.73(1H,d)
73		^{1}H-NMR($CDCl_3$)δ; 0.95(3H,t), 1.04∿2.10(13H,m), 3.68∿4.00 (2H,m), 4.28∿4.60(2H,m), 4.48(2H,s), 5.46(3H,t), 7.74(5H,s), 7.48∿7.72(1H,m), 8.57(1H,d), 8.71(1H,d)

Table 6 (cont'd)

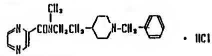
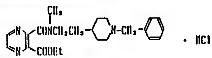
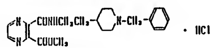
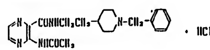
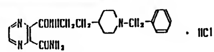
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
74		^{1}H-NMR($CDCl_3$)δ; 1.00∿2.06(9H,m), 2.70∿2.92(2H,m), 3.00∿3.13(2H,m), 3.34∿3.60(4H,m), 7.26 (5H,s), 8.52(1H,d), 8.62(1H,d), 8.91(1H,d)
75		^{1}H-NMR($CDCl_3$)δ; 0.92∿2.06(9H,m), 1.40(3H,t), 2.64∿2.91 (2H,m), 3.12(3H,s), 3.36∿3.72(4H,m), 4.46(2H,q), 7.28(5H,s), 8.73(2H,d)
76		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.16(9H,m), 2.72∿3.02(2H,m), 3.10 3.62(2H,m), 3.51(2H,s), 4.04(3H,s), 7.2∿7.48(5H,m), 7.48∿7.80(1H,m), 8.60 (1H,d), 8.69(1H,d)
77		^{1}H-NMR($CDCl_3$)δ; 1.04∿2.28(9H,m), 2.36(3H,s), 3.44(2H,s), 3.50∿3.76(2H,m), 7.12∿7.25(5H,m), 9.03(2H,s)
78		^{1}H-NMR($CDCl_3$)δ; 0.96∿2.16(9H,m), 2.56∿3.00(2H,m), 3.00∿3.40(2H,t), 3.44(2H,s), 7.20(5H,s), 8.02(2H,s)

Table 6 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
79	 · HCl	^{1}H-NMR($CDCl_3$)δ; 1.04~2.24(9H,m), 2.76~3.00(2H,m), 3.34~3.66(2H,m), 3.50(2H,s), 5.04~5.28(1H,m), 7.10~7.36(5H,m), 7.48~7.72(1H,m), 8.54(1H,d), 8.54(1H,d)
80	 · 2HCl	^{1}H-NMR($CDCl_3$)δ; 1.08~2.16(9H,m), 2.76~3.06(2H,m), 3.24~3.68(2H,m), 3.54(2H,s), 7.18~7.46(6H,m), 8.00~8.18(1H,m), 8.28~8.54(1H,m)
81	 · HCl	^{1}H-NMR($CDCl_3$)δ; 0.98~2.16(9H,m), 2.60~3.00(2H,m), 3.14(3H,s), 3.32~3.72(4H,m), 7.04~7.32(5H,m), 7.60~7.82(1H,m), 7.84~8.15(2H,m), 9.05(1H,s)
82	 · 2HCl	^{1}H-NMR($CDCl_3$)δ; 1.00~2.05(9H,m), 2.56~3.00(2H,m), 3.08, 3.12(total 3H, each s), 3.30~3.70(4H,m), 7.18,7.21(total 5H, each s), 7.33~8.22(6H,m)
83	 · 2HCl	^{1}H-NMR($CDCl_3$)δ; 1.11~2.09(9H,m), 2.87(2H,bd), 3.20~3.62(4H,m), 7.22(5H,s), 7.41~7.64(3H,m), 8.00(1H,dd), 8.20(2H,s) mol. form.: $C_{24}H_{27}N_3O \cdot 2HCl$
84	 · 2HCl	m.p.(°C); 197.5~198.5 elem. anal.: $C_{24}H_{27}N_3O \cdot 2HCl$ C H N calcd. (%) 64.57 6.55 9.41 found (%) 64.26 6.58 9.35
85	 · HCl	m.p. (°C); 174~176.5 elem. anal.: $C_{24}H_{28}N_4O_2 \cdot HCl$ C H N calcd. (%) 65.37 6.63 12.71 found (%) 64.96 6.63 12.60 1/2H_2O(%) 64.97 6.66 12.63

Table 7

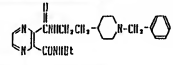
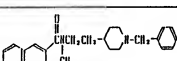
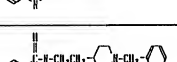
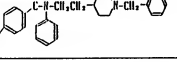
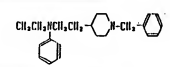
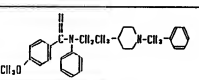
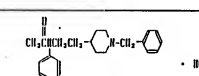
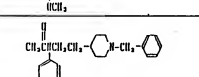
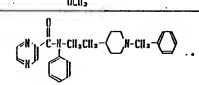
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
86	 · HCl	^{1}H-NMR($CDCl_3$) δ; 0.96∿2.24(9H,m), 1.25(3H,t), 2.60∿3.08(2H, m), 3.44(2H,s), 3.12∿3.15(4H,m), 7.20 (5H,s), 8.44(2H,s)
87	 · 2HCl	^{1}H-NMR($CDCl_3$) δ; 1.00∿2.08(9H,m), 2.70(2H,bd), 3.04(3H,bd), 3.40(2H,bd), 7.17(5H,s), 7.40∿7.61(2H,m), 7.66∿7.82(2H,m), 7.99∿8.11(2H,m), 7.83 (1H,d) mol. form.; $C_{25}H_{29}N_3O \cdot 2HCl$
88	 · HCl	^{1}H-NMR($CDCl_3$) δ; 1.1∿2.1(9H,m), 2.7∿3.0(2H,m), 3.50(2H,s), 3.90(2H,t), 6.9∿7.6(12H,m), 8.03(2H,d) mol. form.; $C_{27}H_{29}N_3O_3 \cdot HCl$
89	 · HCl	^{1}H-NMR($CDCl_3$) δ; 1.1∿2.1(9H,m), 2.7∿3.0(2H,m), 3.48(2H,s), 3.8∿4.0(2H,m), 6.6∿7.4(14H,m) mol. form.; $C_{27}H_{29}N_2OF \cdot HCl$
90	 · HCl	^{1}H-NMR($CDCl_3$) δ; 1.1∿2.2(9H,m), 2.7∿3.0(2H,m), 3.48(2H,s), 3.89(2H,m), 6.8∿7.4(15H,m) mol. form.; $C_{27}H_{30}N_2O \cdot HCl$

Table 7 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
91		^{1}H-NMR($CDCl_3$)δ; 1.16(3H,t), 1.1∿2.2(9H,m), 2.7∿3.0(2H,m), 3.1∿3.4(4H,m), 3.52(2H,s), 6.5∿7.4(10H,m) mol. form.; $C_{22}H_{30}N_2$
92		^{1}H-NMR($CDCl_3$)δ; 1.10∿2.06(9H,m), 2.82(2H,bd), 3.43(2H,s), 3.58(3H,s), 3.88(2H,bt), 6.50(2H,d), 6.69(2H,d), 6.98(5H,bs), 7.19(5H,s) mol. form.; $C_{28}H_{32}N_2O_2$
93	 · HCl	^{1}H-NMR($CDCl_3$)δ; 1.78(3H,s), 1.0∿2.1(9H,m), 2.6∿3.0(2H,m), 3.43(2H,s), 3.75(2H,m), 3.73(3H,s), 6.64(4H,dd), 7.26(5H,s) mol. form.; $C_{23}H_{30}N_2O_2$·HCl
94		^{1}H-NMR($CDCl_3$)δ; 1.1∿2.1(9H,m), 1.84(3H,s), 2.7∿3.0(2H,m), 3.44(2H,s), 3.5∿3.8(2H,m), 3.80(3H,s), 6.5∿6.9(3H,m), 7.22(6H,s) mol. form.; $C_{23}H_{30}N_2O_2$
95	 · · HCl	^{1}H-NMR($CDCl_3$)δ; 1.16∿2.16(9H,m), 2.68∿2.98(2H,m), 3.49(2H,s), 3.84∿4.09(2H,t), 6.91∿7.40 (10H,m), 8.22∿8.44(2H,m), 8.62(1H,s)

EP 0 742 207 A1

Table 7 (cont'd)

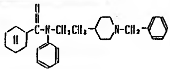
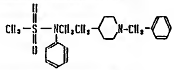
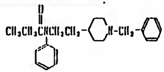
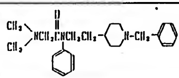
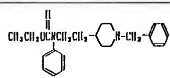
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
96	 · HCl	^{1}H-NMR($CDCl_3$)δ; 1.98∿2.26(20H,m), 2.85(2H,bd), 3.48(2H,s), 3.62(2H,bt), 6.96∿7.40(9H,m) mol. form.; $C_{27}H_{36}N_2O\cdot HCl$
97	 · HCl	^{1}H-NMR($CDCl_3$)δ; 0.90∿2.10(9H,m), 2.65∿2.98(2H,m), 2.83 (3H,s), 3.47(2H,s), 3.52∿3.92(2H,m), 7.26(5H,s), 7.26∿7.43(5H,m) mol. form.; $C_{21}H_{20}N_2O_2S.HCl$
98	 · HCl	^{1}H-NMR($CDCl_3$)δ; 1.02(3H,t), 1.10∿2.00(9H,m), 1.98(2H,q), 2.80(2H,bd), 3.43(2H,s), 3.55∿3.80(2H,m), 6.97∿7.40(5H,m), 7.20(5H,s) mol. form.; $C_{23}H_{30}N_2O.HCl$
99	 · 2HCl	^{1}H-NMR($CDCl_3$)δ; 1.0∿2.1(9H,m), 2.18(6H,s), 2.6∿3.0(4H,m), 3.38(2H,s), 3.4∿3.8(2H,m), 6.9∿7.5(10H,m) mol. form.; $C_{24}H_{33}N_3O\cdot 2HCl$
100	 · HCl	^{1}H-NMR($CDCl_3$)δ; 1.17(3H,t), 1.1∿2.1(9H,m), 2.6∿2.9(2H,m), 3.40(2H,s), 3.4∿3.8(2H,m), 4.08(2H,t), 7.19(10H,s) mol. form.; $C_{23}H_{30}N_2O_2\cdot HCl$

Table 7 (cont'd)

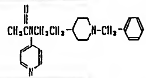
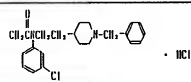
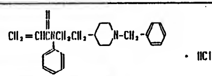
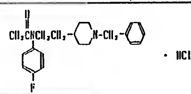
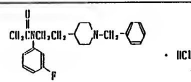
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
101		^{1}H-NMR($CDCl_3$)δ; 1.24∿1.81(9H,m), 2.0(3H,s), 2.82∿2.96 (2H,d), 3.54(2H,s), 3.80(2H,m), 7.18 (2H,dd), 7.36(5H,s), 8.70(2H,dd) mol. form.; $C_{21}H_{27}N_3O$
102		^{1}H-NMR($CDCl_3$)δ; 1.83(3H,s), 1.0∿2.2(9H,m), 2.6∿3.0(2H,m), 3.43(2H,s), 3.66(3H,t), 6.8∿7.4(9H,m) mol. form.; $C_{22}H_{27}N_2OCl\cdot HCl$
103		^{1}H-NMR($CDCl_3$)δ; 1.16∿2.06(9H,m), 2.83(2H,bd), 3.47(2H,s), 3.78(2H,bt), 5.42(1H,dd), 5.90(1H,dd), 6.20(1H,dd), 6.99∿7.40(10H,m) mol. form.; $C_{23}H_{28}N_2O\cdot HCl$
104		^{1}H-NMR-($CDCl_3$)δ; 1.14∿2.03(12H,m), 2.83(2H,bd), 3.44(2H,s), 3.64(2H,bt), 7.00(2H,s), 7.08(2H,s), 7.22(5H,s) mol. form.; $C_{22}H_{27}FN_2O\cdot HCl$
105		^{1}H-NMR($CDCl_3$)δ; 1.15∿1.95(12H,m), 2.84(2H,bd), 3.65(2H,s), 3.67(2H,bt), 6.75∿7.07(3H,m), 7.23(6H,s) mol. form.; $C_{22}H_{27}FN_2O\cdot HCl$

Table 7 (cont'd)

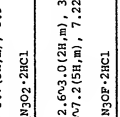
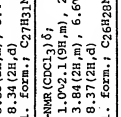
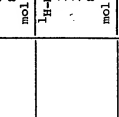
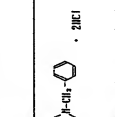
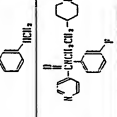
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
106	 · 2HCl	^{1}H-NMR(CDCl$_3$)δ; 1.0~2.1(9H,m), 2.6~3.0(2H,m), 3.43(2H,s), 3.85(2H,m), 6.4~6.7(3H,m), 6.9~7.3(8H,m), 8.34(2H,d) mol. form.; $C_{27}H_{31}N_3O_2 \cdot 2HCl$
107	 · 2HCl	^{1}H-NMR(CDCl$_3$)δ; 1.0~2.1(9H,m), 2.6~3.0(2H,m), 3.41(2H,s), 3.84(2H,m), 6.6~7.2(5H,m), 7.22(5H,s), 8.37(2H,d) mol. form.; $C_{26}H_{28}N_3OF \cdot 2HCl$
108	 · 2HCl	^{1}H-NMR(CDCl$_3$)δ; 1.0~2.1(9H,m), 2.6~3.0(2H,m), 3.43(2H,s), 3.57(6H,s), 3.83(2H,m), 6.0~6.2(3H,m), 7.0~7.4(7H,m), 8.35(2H,d)
109	 · HCl	^{1}H-NMR(CDCl$_3$)δ; 1.77(3H,s), 1.0~2.1(9H,m), 2.32(3H,s), 2.6~2.9(2H,m), 3.40(2H,s), 3.63(2H,m), 6.7~7.3(9H,m) mol. form.; $C_{28}H_{33}N_3O_3 \cdot HCl$
110	 · HCl	^{1}H-NMR(CDCl$_3$)δ; 1.85(3H,s), 1.1~2.2(9H,m), 2.6~3.0(2H,m), 3.42(2H,s), 3.60(2H,m), 3.75(6H,s), 6.20(2H,d), 6.35(1H,m), 7.18(5H,s) mol. form.; $C_{24}H_{32}N_2O_3 \cdot HCl$

Table 7 (cont'd)

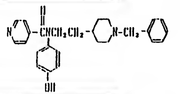
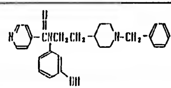
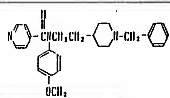
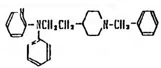
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
111	 · 2HCl	^1H-NMR ($CDCl_3$) δ; 1.1∼2.1 (9H, m), 2.6∼3.0 (2H, m), 3.50 (2H, s), 3.83 (2H, m), 6.58 (4H, dd), 7.04 (2H, d), 7.19 (5H, s), 8.28 (2H, d) mol. form.; $C_{26}H_{29}N_3O_2 \cdot 2HCl$
112	 · 2HCl	^1H-NMR ($CDCl_3$) δ; 1.07∼2.35 (9H, m), 2.99 (2H, bd), 3.62 (2H, s), 3.81 (2H, bt), 6.31∼6.56 (3H, m), 6.84∼7.11 (3H, m), 7.25 (5H, s), 8.31 (2H, bs) mol. form.; $C_{26}H_{29}N_3O_2 \cdot 2HCl$
113	 · 2HCl	^1H-NMR ($CDCl_3$) δ; 1.1∼2.1 (9H, m), 2.6∼3.0 (2H, m), 3.44 (2H, s), 3.68 (3H, m), 3.85 (2H, m), 6.78 (4H, dd), 7.02 (2H, d), 7.23 (5H, s), 8.37 (2H, d) mol. form.; $C_{27}H_{31}N_3O_2 \cdot 2HCl$
114	 · 2HCl	^1H-NMR ($CDCl_3$) δ; 7.20 (11H, m), 8.05 (1H, m), 1.2∼1.83 (9H, m), 2.65∼2.81 (2H, d), 3.4 (2H, s), 3.90 (2H, m), 6.20∼6.52 (2H, m) mol. form.; $C_{25}H_{29}N_3 \cdot 2HCl$

Table 8

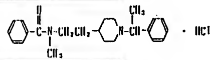
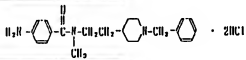
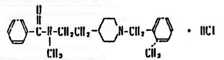
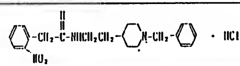
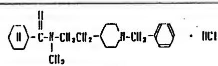
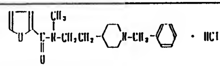
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
115		^{1}H-NMR($CDCl_3$)δ; 0.80∿2.12(12H,m), 2.52∿3.64(8H,m), 7.06∿7.52(10H,m)
116		^{1}H-NMR($CDCl_3$)δ; 1.08∿2.10(9H,m), 2.80∿2.92(2H,d), 3.00 (3H,s), 3.34∿3.50(4H,m), 3.90(2H,s), 6.60(2H,d), 7.21∿7.28(7H,m) mol. form.; $C_{22}H_{29}N_3O\cdot 2HCl$
117		^{1}H-NMR($CDCl_3$)δ; 1.0∿2.1(9H,m), 2.31(3H,s), 2.5∿3.1(5H,m), 3.1∿3.6(4H,m), 7.0∿7.4(9H,m) mol. form.; $C_{23}H_{30}N_2O\cdot HCl$
118		^{1}H-NMR($CDCl_3$)δ; 1.0∿2.2(9H,m), 2.7∿3.0(2H,m), 3.29(2H,m), 3.50(2H,s), 3.81(2H,s), 5.8(1H,s), 7.25 (5H,s), 7.3∿7.7(3H,m), 8.03(1H,d) mol. form.; $C_{22}H_{27}N_3O_3\cdot HCl$
119		^{1}H-NMR($CDCl_3$)δ; (in free form) 1.10∿2.06(17H,m), 2.10∿2.32(3H,m), 2.96 (3H,s), 3.20∿3.52(4H,m), 4.08∿4.16(2H,d), 7.36∿7.76(5H,m) mol. form.; $C_{22}H_{34}N_2O\cdot HCl$
120		^{1}H-NMR($CDCl_3$)δ; 1.20∿2.08(9H,m), 2.80∿2.92(2H,d), 3.12 (3H,s), 3.46∿3.64(4H,m), 6.42(1H,dd), 7.00(1H,dd), 7.26∿7.45(6H,m) mol. form.; $C_{20}H_{26}N_2O_2\cdot HCl$

Table 8 (cont'd)

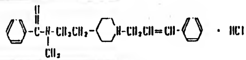
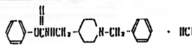
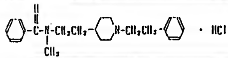
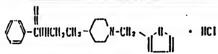
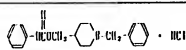
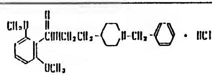
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
121		^{1}H-NMR($CDCl_3$)δ; 1.02∼2.06(9H,m), 2.71∼3.57(9H,m), 6.16∼6.54(2H,m), 7.10∼7.55(10H,m) mol. form.; $C_{24}H_{30}N_2O \cdot HCl$
122		^{1}H-NMR($CDCl_3$)δ; 1.1∼2.1(7H,m), 2.8∼3.05(2H,m), 3.05∼3.15 (2H,m), 3.49(2H,s), 5.1(1H,), 7.0∼7.5 (10H,m) mol. form.; $C_{20}H_{24}N_2O_2 \cdot HCl$
123		^{1}H-NMR($CDCl_3$)δ; 1.00∼3.08(20H,m), 7.22(5H,bs), 7.37(5H,s) mol. form.; $C_{23}H_{30}N_2O \cdot HCl$
124		^{1}H-NMR($CDCl_3$)δ; 1.30∼2.24(9H,m), 2.86(2H,bd), 3.32∼3.60 (4H,m), 6.08∼6.28(2H,m), 7.20∼8.02(6H,m) mol. form.; $C_{19}H_{24}N_2O_2 \cdot HCl$
125		^{1}H-NMR($CDCl_3$)δ; 1.1∼2.2(9H,m), 2.8∼3.1(2H,m), 3.50(4H,s), 7.30(10H,s) mol. form.; $C_{20}H_{23}NO_3 \cdot HCl$
126		^{1}H-NMR($CDCl_3$)δ; (in free form) 1.20∼2.16(9H,m), 2.64∼3.0(2H,bd), 3.46 (2H,s), 3.36∼3.60(2H,m), 3.80(6H,s), 5.60 (1H,bs), 6.50∼6.60(2H,d), 7.16∼7.40(6H,m) moo. form.; $C_{23}H_{30}N_2O_3 \cdot HCl$

Table 8 (cont'd)

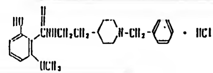
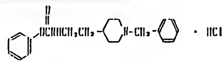
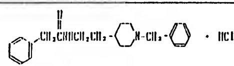
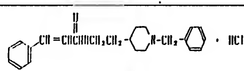
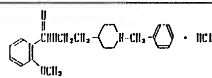
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
127		^{1}H-NMR($CDCl_3$)δ; (in free form) 1.12~2.16(9H,m), 2.76~3.0(2H,bd), 3.48 (2H,s), 3.32~3.60(2H,m), 3.92(3H,s), 6.32~7.40(8H,m), 8.26(1H,bs), 14.0(1H,s) mol. form.; $C_{22}H_{28}N_2O_3 \cdot HCl$
128		^{1}H-NMR($CDCl_3$)δ; 1.1~2.2(9H,m), 2.7~3.0(2H,m), 3.1~3.4(2H, m), 3.46(2H,s), 4.90(1H), 6.9~7.4(10H,m) mol. form.; $C_{21}H_{26}N_2O_2 \cdot HCl$
129		^{1}H-NMR($CDCl_3$)δ; 1.1~2.2(9H,m), 2.7~3.0(4H,m), 3.1~3.6 (2H,m), 3.55(2H,s), 5.5(1H), 7.30(10H,s) mol. form.; $C_{22}H_{28}N_2O \cdot HCl$
130		^{1}H-NMR($CDCl_3$)δ; 1.1~2.2(9H,m), 2.7~3.0(2H,m), 3.2~3.4 (2H,m), 3.40(2H,s), 5.9(1H), 6.39(1H,d), 7.1~7.8(11H,m) mol. form.; $C_{23}H_{28}N_2O \cdot HCl$
131		^{1}H-NMR($CDCl_3$)δ; (in free form) 1.1~2.2(9H,m), 2.6~3.0(2H,bd), 3.44(2H,s), 3.36~3.6(2H,m), 3.90(3H,s), 6.9~8.30 (10H,m) mol. form.; $C_{22}H_{20}N_2O_2 \cdot HCl$

Table 8 (cont'd)

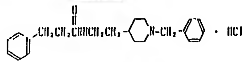
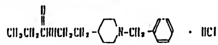
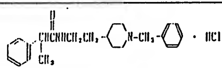
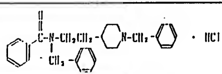
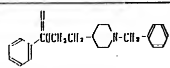
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
132		^{1}H-NMR(CDCl$_3$)δ; 1.1∿2.2(9H,m), 2.3∿2.7(4H,m), 2.7∿3.0(2H, m), 3.0∿3.5(4H,m), 6.1(1H), 7.0∿7.7(10H,m) mol. form.; $C_{23}H_{30}N_2O \cdot HCl$
133		^{1}H-NMR(CDCl$_3$)δ; 1.17(3H,t), 1.2∿2.1(9H,m), 2.17(2H,q), 2.7∿3.0(2H,m), 3.1∿3.4(2H,m), 3.45(2H,s), 5.3(1H), 7.21(5H,s) mol. form., $C_{17}H_{26}N_2O \cdot HCl$
134		^{1}H-NMR(CDCl$_3$)δ; 1.1∿2.0(12H,m), 2.6∿3.0(2H,m), 3.0∿3.3 (2H,m), 3.41(2H,s), 3.3∿3.4(1H,m), 7.23 (10H,s) mol. form.; $C_{23}H_{30}N_2O \cdot HCl$
135		^{1}H-NMR(CDCl$_3$)δ; 0.90∿2.10(9H,m), 2.78(2H,bd), 3.00∿3.70 (2H,m), 3.43(2H,s), 4.40∿4.85(2H,m), 7.27(10H,s), 7.38(5H,s) mol. form.; $C_{28}H_{32}N_2O \cdot HCl$
136		^{1}H-NMR(CDCl$_3$)δ; 1.0∿2.1(9H,m), 2.7∿3.0(2H,m), 3.48(2H,s), 4.36(2H,t), 7.0∿7.7(8H,m), 7.8∿8.2(2H,m) mol. form.; $C_{21}H_{25}NO_2$

Table 8 (cont'd)

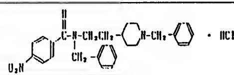
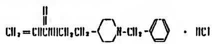
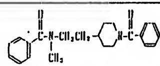
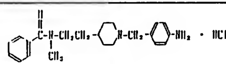
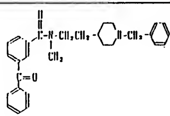
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
137		^{1}H-NMR(CDCl$_3$)δ; 0.86∿1.90(9H,m), 2.56∿3.05(4H,m), 3.38 (2H,d), 4.56(1H,s) 4.68(1H,s), 7.00∿7.56 (12H,m), 8.10(2H,m) mol. form.; $C_{28}H_{31}N_3O_3 \cdot HCl$
138		^{1}H-NMR(CDCl$_3$)δ; 1.0∿2.1(9H,m), 2.7∿3.0(2H,m), 3.1∿3.4 (2H,m), 3.47(2H,s), 5.58(1H,dd), 5.9∿6.1 (2H,m), 7.29(5H,s) mol. form.; $C_{17}H_{24}N_2O \cdot HCl$
139		^{1}H-NMR(CDCl$_3$)δ; 1.00∿4.08(16H,m), 7.38(10H,s) mol. form.; $C_{22}H_{26}N_2O_2$
140		^{1}H-NMR(CDCl$_3$)δ; 0.90∿2.10(9H,m), 2.55∿3.50(7H,m), 3.52(2H,s), 7.38(5H,s), 7.80(4H,ABq) mol. form.; $C_{22}H_{27}N_3O_3 \cdot HCl$
141		^{1}H-NMR(CDCl$_3$)δ; 0.96∿2.08(3H,m), 2.60∿3.10(6H,m), 3.48(2H,d), 7.16∿7.92(14H,m)

Table 8 (cont'd)

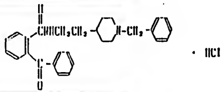
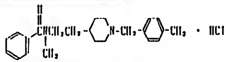
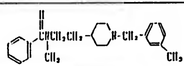
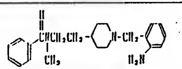
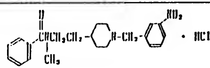
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
142		^{1}H-NMR($CDCl_3$)δ; 0.80∿2.04(9H,m), 2.48∿2.88(2H,m), 3.12∿3.52(4H,m) 7.03∿7.72(14H,m)
143		^{1}H-NMR($CDCl_3$)δ; 1.01∿2.01(19H,m), 2.33(3H,s), 2.63∿3.04 (5H,bd), 3.42(2H,bd), 7.15(4H,bs), 7.35(5H,s) mol. form.; $C_{23}H_{30}N_2O\cdot HCl$
144		^{1}H-NMR($CDCl_3$)δ; 1.00∿1.96(11H,m), 2.30(3H,s), 3.38(2H,bd), 7.02(4H,bd), 7.28(5H,s) mol. form.; $C_{23}H_{30}N_2O$
145		^{1}H-NMR($CDCl_3$)δ; 0.90∿2.18(9H,m), 2.52∿3.70(7H,m), 3.72 (2H,s), 7.10∿7.88(4H,m), 7.38(5H,s) mol. form.; $C_{22}H_{27}N_3O_3$
146		m.p. (°C); 216∿217 (dec.) elem. anal.: $C_{22}H_{27}N_3O_3\cdot HCl$ C H N calcd. (%) 63.23 6.75 10.05 found (%) 62.95 6.69 9.88

Table 8 (cont'd)

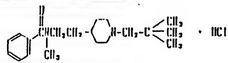
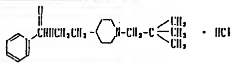
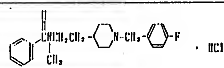
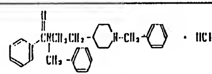
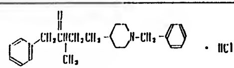
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
147		^{1}H-NMR($CDCl_3$)δ; 0.82(9H,s), 1.02~2.28(9H,m), 2.60~3.60 (9H,m), 7.28(5H,s) mol. form.; $C_{20}H_{32}N_2O\cdot HCl$
148		^{1}H-NMR($CDCl_3$)δ; 0.85(9H,s), 1.12~2.28(9H,m), 2.76(2H,bd), 3.42(2H,q), 7.38(3H,m), 7.67(2H,dd) mol. form.; $C_{19}H_{30}N_2O\cdot HCl$
149		^{1}H-NMR($CDCl_3$)δ; 1.0~2.2(9H , m), 1.6~2.1(5H,m), 2.2~2.6 (4H,m), 6.8~7.7(9H,m) mol. form.; $C_{22}H_{27}N_2O\cdot HCl$
150		^{1}H-NMR($CDCl_3$)δ; 1.00~2.05(9H,m), 2.08,2.12(total 3H, each s), 2.82(2H,bd), 3.03~3.43(2H,m), 3.44(2H, s), 4.47,4.56(total 3H, each s), 7.35(10H, s) mol. form.; $C_{23}H_{30}N_2O\cdot HCl$
151		^{1}H-NMR($CDCl_3$)δ; 1.00~2.08(9H,m), 2.78(2H,bd), 2.88(3H,s), 3.10~3.45(2H,m), 3.43(2H,s), 3.57(2H,s), 7.22(10H,s) mol. form.; $C_{23}H_{30}N_2O\cdot HCl$

Table 8 (cont'd)

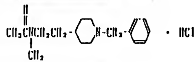
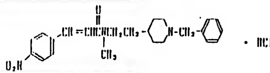
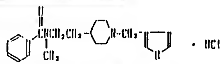
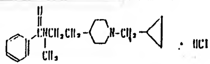
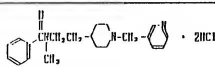
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
152		^{1}H-NMR ($CDCl_3$) δ; 1.00~2.00 (9H,m), 2.03 (3H,s), 2.80 (2H,bd), 2.88, 2.91 (total 3H, each s), 3.05~3.40 (2H,m), 3.43 (3H,s), 7.20 (5H,s) mol. form.; $C_{17}H_{26}N_2O \cdot HCl$
153		^{1}H-NMR ($CDCl_3$) δ; 1.1~2.2 (9H,m), 2.6~3.2 (5H,m), 3.2~3.6 (4H,m), 6.8~7.1 (1H,m), 7.3 (5H,s), 7.5~7.8 (3H,m), 8.24 (2H,d) mol. form.; $C_{26}H_{29}N_3O_3 \cdot HCl$
154		^{1}H-NMR ($CDCl_3$) δ; 1.00~2.08 (10H,m), 2.72~3.08 (5H,m), 3.33 (2H,bd), 6.16 (1H,bs), 7.07 (7H,bs) mol. form.; $C_{20}H_{26}N_2O_2 \cdot HCl$
155		^{1}H-NMR ($CDCl_3$) δ; 0.15 (2H,m), 0.56 (2H,m), 0.90~2.23 (10H,m), 3.00 (5H,m), 3.34 (4H,m), 7.40 (5H,s) mol. form.; $C_{19}H_{28}N_2O \cdot HCl$
156		^{1}H-NMR ($CDCl_3$) δ; 1.00~2.02 (9H,m), 2.64~3.00 (5H,m), 3.41 (4H,m), 7.15 (1H,m), 7.27 (5H,s), 7.50 (1H,d), 8.41 (2H,m) mol. form.; $C_{21}H_{27}N_3O \cdot 2HCl$

Table 8(cont'd)

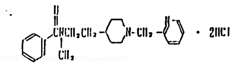
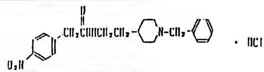
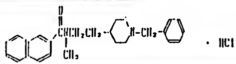
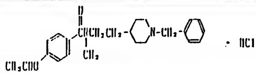
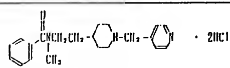
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
157		^{1}H-NMR($CDCl_3$)δ; 1.04∿1.04(11H,m), 2.64∿3.00(5H,m), 3.58 (2H,s), 7.01(1H,m), 7.27(5H,s), 7.58 (2H,m), 8.44(1H,d) mol. form.; $C_{21}H_{27}N_3O \cdot 2HCl$
158		^{1}H-NMR($CDCl_3$)δ; 1.00∿2.00(4H,m), 2.83(2H,bd), 3.24(2H,bd), 3.45(2H,s), 3.59(2H,s), 5.85(1H,bs), 7.27(5H,s), 7.77(4H,ABq) mol. form.; $C_{22}H_{27}N_3O_3 \cdot HCl$
159		^{1}H-NMR($CDCl_3$)δ; 1.0∿2.1(9H,m), 2.6∿3.2(5H,m), 3.2∿3.7 (4H,m), 7.25(5H,s), 7.3∿8.1(7H,m) mol. form.; $C_{26}H_{30}N_2O \cdot HCl$
160		^{1}H-NMR($CDCl_3$)δ; 1.00∿2.10(9H,m), 2.25(3H,s), 2.81(2H,bd), 2.97(3H,bs), 3.10∿3.45(2H,m), 3.43(2H,s), 7.23(4H,ABq), 7.27(5H,s) mol. form.; $C_{24}H_{30}N_2O_3 \cdot HCl$
161		^{1}H-NMR($CDCl_3$)δ; 1.06∿1.92(9H,m), 2.70∿2.99(5H,m), 3.44 (2H,s), 7.22(2H,d), 7.38(5H,s), 8.50(2H,d) mol. form.; $C_{21}H_{27}N_3O \cdot 2HCl$

Table 8 (cont'd)

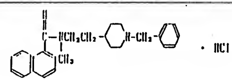
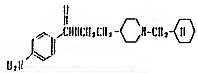
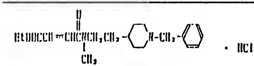
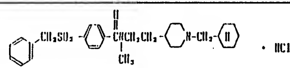
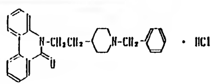
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
162		^{1}H-NMR(CDCl$_3$)δ; 0.90~1.05(9H,m), 2.70(3H,s), 3.00(2H,d), 3.22(2H,s), 3.37(1H,s), 3.46(1H,s), 7.18~7.60(9H,m), 7.78(3H,m) mol. form.; $C_{26}H_{30}N_2O \cdot HCl$
163		^{1}H-NMR(CDCl$_3$)δ; 0.7~2.2(20H,m), 2.8~3.2(4H,), 3.55(2H,m), 6.95(1H,s), 8.02(2H,d), 8.34(2H,d) mol. form.; $C_{21}H_{31}N_3O_2$
164		^{1}H-NMR(CDCl$_3$)δ; 1.1~2.1(12H,m), 2.7~3.1(5H,m), 3.2~3.6(4H,m), 4.22(2H,q), 6.7(1H,m), 7.2~7.4(6H,m) mol. form.; $C_{21}H_{30}N_2O_3 \cdot HCl$
165		^{1}H-NMR(CDCl$_3$)δ; 0.56~3.36(23H,m), 3.40~3.68(2H,m), 4.28(2H,s), 7.18(5H,s), 8.34(2H,d), 8.58(2H,d)
166		^{1}H-NMR(CDCl$_3$)δ; 1.16~2.12(9H,m), 2.89(2H,bd), 3.47(2H,s), 4.35(2H,bt), 7.08~7.74(11H,m), 8.08(1H,bd), 8.23(1H,dd)

Table 8 (cont'd)

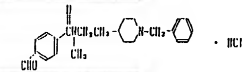
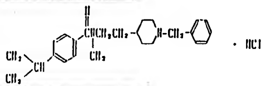
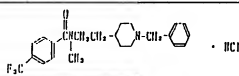
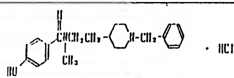
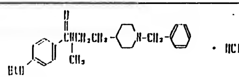
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
167		^{1}H-NMR(CDCl$_3$)δ; 1.08∼1.94(9H,m), 2.68∼3.02(7H,m), 3.40 (2H,d), 7.27(5H,s), 7.41(2H,d), 7.78(2H,d), 10.0(1H,s) mol. form.; $C_{23}H_{28}N_2O_2 \cdot HCl$
168		^{1}H-NMR(CDCl$_3$)δ; 1.10∼1.98(15H,m), 2.77∼2.98(6H,m), 3.12∼3.46(4H,m), 7.26(9H,m) mol. form.; $C_{25}H_{34}N_2O \cdot HCl$
169		^{1}H-NMR(CDCl$_3$)δ; 1.00∼2.00(9H,m), 2.60∼3.00(7H,m), 3.45 (2H,m), 6.95(2H,d), 7.26(5H,s), 7.90(2H,d) mol. form.; $C_{23}H_{27}N_2OF_3 \cdot HCl$
170		^{1}H-NMR(CDCl$_3$)δ; 1.00∼2.10(3H,m), 2.87(2H,bd), 2.99(3H,s), 3.10∼3.50(2H,m), 3.48(3H,s), 6.35∼7.35 (5H,m), 7.83(5H,s) mol. form.; $C_{22}H_{28}N_2O_2 \cdot HCl$
171		^{1}H-NMR(CDCl$_3$)δ; 1.10∼1.88(12H,m), 2.80(2H,d), 2.98(3H,s), 3.23∼3.44(4H,m), 4.02(2H,m), 6.84(2H,d), 7.26(7H,m) mol. form.; $C_{24}H_{32}N_2O_2 \cdot HCl$

Table 8 (cont'd)

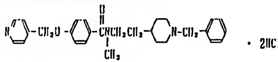
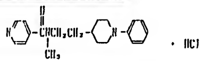
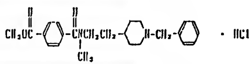
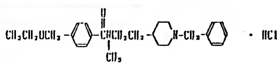
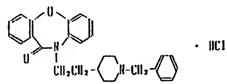
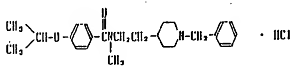
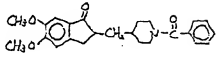
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
172		^{1}H-NMR($CDCl_3$)δ; 1.00∼2.08(9H,m), 2.83(2H,bd), 2.98(3H,s), 3.12∼3.50(2H,m), 3.47(2H,s), 5.08(2H,s), 7.15(4H,ABq), 7.38(5H,s), 7.96(2H,ABq)
173		^{1}H-NMR($CDCl_3$)δ; 1.04∼1.98(7H,m), 2.20∼3.80(7H,m), 6.60∼7.34(7H,m), 8.67(2H,d)
174		^{1}H-NMR($CDCl_3$)δ; 0.90∼2.20(11H,m), 2.60∼3.30(2H,m), 2.85, 3.03(total 3H, each bs), 3.48,3.55(total 2H, each bs), 3.88(3H,s), 7.19,7.21(total 5H, each s), 7.67(4H,ABq) mol. form.; $C_{24}H_{30}N_2O_2 \cdot HCl$
175		^{1}H-NMR($CDCl_3$)δ; 0.90∼2.06(9H,s), 2.70∼3.02(10H,m), 3.20∼3.62(4H,m), 4.50(2H,s), 7.21∼7.30(9H,d) mol. form.; $C_{25}H_{34}N_2O_2 \cdot HCl$

Table 8 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
176		^{1}N-NMR ($CDCl_3$) δ; 9.90∿2.10 (9H,m), 2.81 (2H,bd), 3.45 (2H,s), 4.11 (2H,t), 6.98∿7.82 (8H,m), 7.21 (5H,s) mol. form.; $C_{27}H_{28}N_2O_2 \cdot HCl$
177		^{1}H-NMR ($CDCl_3$) δ; 1.29 (3H,s), 1.40 (3H,s), 1.40∿2.20 (9H,m), 2.83 (2H,bd), 3.00 (3H,s), 3.20∿3.50 (2H,m), 3.48 (2H,s), 4.56 (1H, quirtet), 7.08 (4H, ABq), 7.28 (5H,s) mol. form.; $C_{25}H_{34}N_2O_2 \cdot HCl$

Example 178

1-Benzoyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]-methylpineridine



0.85 g of 5,6-dimethoxy-1-indanone and 1.38 g of 1-benzoyl-4-piperidinecarbaldehyde were dissolved in 20 ml of anhydrous THF to obtain a solution. 1.02 g of 28 % sodium methylate was added to the solution at 0°C. The obtained mixture was stirred at a room temperature for 2 hours, diluted with ethyl acetate, washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column to obtain 1.23 g of 1-benzoyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine (yield : 71 %).

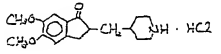
1.23 g of this compound was dissolved in 20 ml of THF, followed by the addition of 0.3 g of 10 % palladium/carbon. After the hydrogenation had been carried out at a room temperature under an ordinary pressure for one day, the catalyst was filtered out and the filtrate was concentrated in a vacuum. The residue was recrystallized from methylene chloride/hexane to obtain 1.10 g of the title compound (yield : 89 %). The characteristics thereof are as follows:

m.p.(°C) : 151 to 152

elemental analysis as $C_{24}H_{27}NO_4$			
	C	H	N
calculated (%)	73.26	6.92	3.56
found (%)	73.30	6.85	3.32

Example 179

4-[(5,6-Dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride



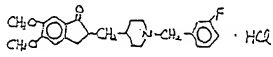
9.00 g of 1-benzoyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine was dissolved in 90 ml of dioxane, followed by the addition of 90 ml of 6N hydrochloric acid. The obtained mixture was heated under reflux for 10 hours and concentrated in a vacuum. The residue was diluted with water and extracted with ethyl acetate. The pH of the aqueous layer was adjusted to 12 with a 50 % aqueous solution of sodium hydroxide and extracted with methylene chloride. The organic layer was washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was converted into its hydrochloride by an ordinary method. The obtained product was recrystallized from methanol/ethanol to obtain 6.30 g of the title compound (yield : 85 %). The characteristics thereof are as follows:

m.p.(°C): 249 to 250 (dec.)

elemental analysis as $C_{17}H_{23}NO_3 \cdot HCl$			
	C	H	N
calculated (%)	62.67	7.42	4.30
found (%)	62.75	7.31	4.52

Example 180

1-(3-Fluorobenzyl)-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride



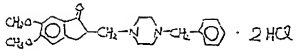
0.25 g of 4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine was dissolved in 6 ml of THF, followed by the addition of 0.29 ml of triethylamine and 0.13 ml of 3-fluorobenzyl bromide. The obtained mixture was heated under reflux for 2 hours and concentrated in a vacuum. The residue was diluted with ethyl acetate, washed with a 10 % aqueous solution of sodium carbonate and a saturated aqueous solution of common salt successively, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method. The obtained product was recrystallized from methylene chloride/IPE to obtain 0.27 g of the title compound (yield : 72 %). The characteristics thereof are as follows:

m.p.(°C): 230 to 232 (dec.)

elemental analysis as $C_{24}H_{28}NO_3 \cdot HCl$			
	C	H	N
calculated(%)	66.43	6.74	3.23
found(%)	66.18	6.79	3.11

Example 181

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine dihydrochloride



1.00 g of 5,6-dimethoxy-1-indanone, 0.31 g of paraformaldehyde and 0.90 ml of 1-benzylpiperazine were suspended in a mixture comprising 30 ml of ethanol and 2 ml of water. The pH of the obtained suspension was adjusted to 3 with concentrated hydrochloric acid, heated under reflux for 3 hours, cooled by allowing to stand and filtered to obtain a white solid. This solid was suspended in methylene chloride, washed with a 10 % aqueous solution of sodium carbon-

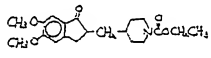
ate and a saturated aqueous solution of common salt successively, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method. The product was recrystallized from methanol to obtain 0.55 g of the title compound (yield : 23 %). The characteristics thereof are as follows:

m.p.(°C) 227 to 228 (dec.)

elemental analysis as $C_{23}H_{29}N_2O_3 \cdot 2HCl$			
	C	H	N
calculated(%)	60.79	6.88	6.16
found(%)	60.31	6.95	6.06

Example 182

4-[(5,6-Dimethoxy-1-indanon)-2-yl]methyl-1-ethoxycarbonylpiperidine



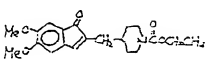
0.50 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine was dissolved in 8 ml or benzene, followed by the addition of 0.15 ml of ethyl chloroformate. The obtained mixture was heated under reflux for 3 hours, diluted with ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous soltuion of common salt successively, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was recrystallized from ethyl acetate/hexane to obtain 0.45 g of the title compound (yield : 94 %). The characteristics thereof are as follows:

m.p.(°C): 132 to 133

elemental analysis as $C_{20}H_{27}NO_5$			
	C	H	N
calculated(%)	66.46	7.53	3.88
found(%)	66.79	7.53	4.00

Example 183

4-[(5,6-Dimethoxy-1-indenon)-2-yl]methyl-1-ethoxycarbonylpiperidine



2.00 g of 4-[(5,6-dimethoxy-1-indanon)-2-yl]methyl-1-ethoxycarbonylpiperidine was dissolved in 30 ml of carbon tetrachloride, followed by the addition of 0.98 g of N-bromosuccinimide and 0.02 g of benzoyl peroxide. The obtained mixture was heated under reflux for 5 hours, diluted with carbon tetrachloride, washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of common salt successively, dried over magnesium sulfate and concentrated in a vacuum.

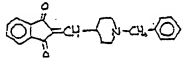
The obtained residue was dissolved in 20 ml of THF, followed by the addition of 1.66 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene. The obtained mixture was heated under reflux for 30 minutes and concentrated in a vacuum. The residue was diluted with ethyl acetate, washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column to obtain 1.12 g of the title compound as an oil (yield : 56 %).

molecular formula: $C_{20}H_{25}NO_5$

^{1}H-NMR($CDCl_3$)δ; 1.23(3H,t), 1.41--2.90(11H,m), 3.84(3H,S), 3.88(3H,S), 4.10(2H,g), 6.60(1H,S), 6.97(1H,S), 7.03(1H,S).

Example 184

1-Benzyl-4-[(1,3-indanedion)-2-ylidenyl]methylpiperidine



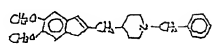
0.17 ml of diisopropylamine was added to 3 ml of anhydrous THF. 0.75 ml of a 1.6 M solution of n-butyllithium in hexane was added to the obtained mixture at 0°C. The obtained mixture was stirred at 0°C for 10 minutes and cooled to -78°C, followed by the addition of a solution of 0.18 g of 1,3-indanedione in 8 ml of anhydrous THF and 0.21 ml of hexamethylphosphoramide. The obtained mixture was stirred at -78°C for 15 minutes, followed by the addition of a solution of 0.35 g of 1-benzyl-4-piperidinecarbaldehyde in 3 ml of anhydrous THF. The obtained mixture was gradually heated to a room temperature, stirred at that temperature overnight, diluted with methylene chloride, washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was recrystallized from methylene chloride/IPE to obtain 0.12 g of the title compound (yield : 29 %). The characteristics thereof are as follows:

m.p.(°C): 173 to 174 (dec.)

elemental analysis as $C_{22}H_{21}NO_2$			
	C	H	N
calculated(%)	79.73	6.39	4.23
found(%)	79.43	6.20	4.31

Example 185

1-Benzyl-4-[(5,6-dimethoxyinden)-2-yl]methylpiperidine hydrochloride



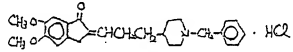
0.24 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanol)-2-yl]methylpiperidine was dissolved in 5 ml of methylene chloride, followed by the addition of a 10 % solution of hydrochloric acid in ethyl acetate. The obtained mixture was concentrated in a vacuum. The obtained residue was recrystallized from methylene chloride/IPE to obtain 0.24 g of the title compound (yield : 95 %). The characteristics thereof are as follows:

m.p.(°C): 216 to 217 (dec.)

elemental analysis as $C_{24}H_{29}NO_2 \cdot HCl$			
	C	H	N
calculated(%)	72.07	7.56	3.50
found(%)	71.82	7.63	3.33

Example 186

1-Benzyl-4-[3-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]]proovlpiperidine hydrochloride



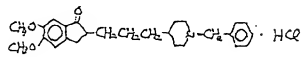
0.31 ml of diisopropylamine was added to 5 ml of anhydrous THF. 1.39 ml of a 1.6 M solution of n-butyllithium in hexane was further added to the obtained mixture at 0°C. The obtained mixture was stirred at 0°C for 10 minutes and cooled to -78°C, followed by the addition of a solution of 0.39 g of 5,6-dimethoxy-1-indanone in 5 ml of anhydrous THF and 0.35 ml of hexamethylphosphoramide. The obtained mixture was stirred at -78°C for 15 minutes, followed by the addition of a solution of 0.50 g of 3-(1-benzyl-4-piperidine)propionaldehyde in 5 ml of anhydrous THF. The obtained mixture was gradually heated to a room temperature, stirred at that temperature for 3 hours, diluted with ethyl acetate, washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method of obtain 0.55 g of the title compound as an oil (yield : 61 %).

molecular formula : $C_{26}H_{31}NO_3 \cdot HCl$

^{1}H-NMR($CDCl_3$)δ; 1.10~3.00(13H,m), 3.45(2H,S), 3.50(2H,S), 3.90(3H,S), 3.95(3H,S), 6.58~7.20 (3H,m), 7.27(5H,S).

Example 187

1-Benzyl-4-[3-[(5,6-dimethoxy-1-indanon)-2-yl]]propylpiperidine hydrochloride



0.40 g of 1-benzyl-4-[3-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]]propylpiperidine was dissolved in 15 ml of THF, followed by the addition of 0.1 g of 10 % palladium/carbon. After the hydrogenation had been carried out at a room temperature under an ordinary pressure for 2 hours, the catalyst was filtered out and the filtrate was concentrated in a vacuum. The residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method to obtain 0.37 g of the title compound as an oil (yield : 84 %).

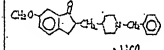
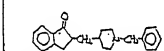
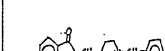
molecular formula: $C_{26}H_{33}NO_3 \cdot HCl$

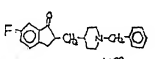
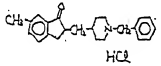
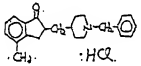
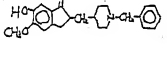
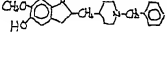
^{1}H-NMR($CDCl_3$)δ; 1.00–3.30(18H, m), 3.38, 3.43 (total 2H, each S), 3.85(3H,S), 3.90(3H,S), 6.77, 6.83 (total 1H, each S), 7.05, 7.10 (total 1H, each S), 7.18, 7.20 (total 5H, each S).

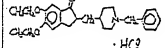
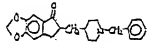
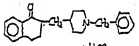
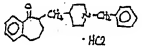
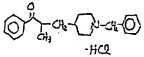
Examples 188 to 249

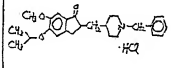
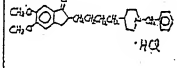
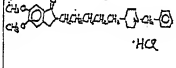
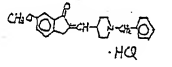
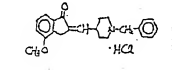
The compounds listed in Table 9 were each synthesized and analyzed.

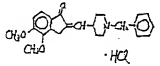
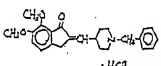
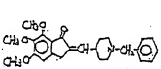
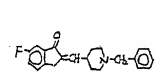
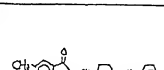
Table 9

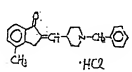
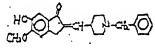
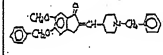
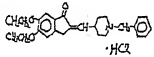
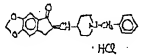
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
188		^{1}H-NMR($CDCl_3$) δ; 1.00∿3.40(14H,m), 3.47(2H,S), 3.78(3H,S), 6.90∿7.50(3H,m), 7.23(5H,S). molecular formula: $C_{23}H_{27}NO_2 \cdot HCl$
189		^{1}H-NMR($CDCl_3$) δ; 1.05∿2.12(9H,m), 2.50∿3.40(5H,m), 3.48(2H,S), 3.88(3H,S), 6.98(1H,q), 7.15∿7.32(2H,m), 7.23(5H,S), molecular formula: $C_{23}H_{27}NO_2 \cdot HCl$
190		m.p.(°C) : 199 to 200 (dec.) elemental analysis as $C_{24}H_{29}NO_3 \cdot HCl$ C H N calculated(%) 69.30 7.27 3.37 found(%) 69.24 7.40 3.38
191		m.p.(°C) : 198 to 199 elemental analysis as $C_{24}H_{29}NO_3 \cdot HCl$ C H N calculated(%) 69.30 7.27 3.37 found(%) 69.15 7.42 3.47
192		m.p.(°C) : 200 to 201 elemental analysis as $C_{25}H_{31}NO_4 \cdot HCl$ C H N calculated(%) 67.33 7.23 3.14 found(%) 67.10 7.16 3.00

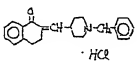
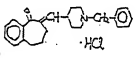
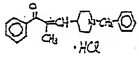
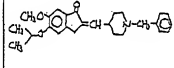
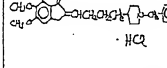
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
193		^{1}H-NMR($CDCl_3$) δ; 1.05∿2.15(9H,m), 2.55∿3.43(5H,m), 3.48(2H,S), 7.23(5H,S), 7.23∿7.43 (3H,m). molecular formula: $C_{22}H_{24}NOF \cdot HCl$
194		m.p.(°C): 175 to 177 elemental analysis as $C_{23}H_{27}NO \cdot HCl$ C H N calculated(%) 74.68 7.63 3.79 found(%) 72.77 7.64 3.62 1/2 H_2O (%) 72.90 7.71 3.70
195		m.p.(°C): 211 to 213 (dec.) elemental analysis as $C_{23}H_{27}NO \cdot HCl$ C H N calculated(%) 74.68 7.63 3.79 found(%) 72.68 7.49 3.70 1/2 H_2O (%) 72.90 7.71 3.70
196		m.p.(°C): 153 to 154 elemental analysis as $C_{23}H_{27}NO_3$ C H N calculated(%) 75.59 7.45 3.83 found(%) 75.77 7.28 3.64
197		m.p.(°C): 170 to 171 (dec.) elemental analysis as $C_{23}H_{27}NO_3$ C H N calculated(%) 75.59 7.45 3.83 found(%) 75.61 7.47 3.55

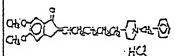
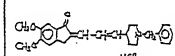
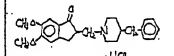
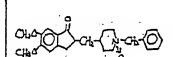
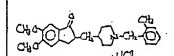
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
198		m.p.(°C): 175 to 176 elemental analysis as $C_{26}H_{33}NO_3 \cdot HCl$ C H N calculated(%) 70.33 7.72 3.15 found(%) 70.20 7.46 3.35
199		m.p.(°C): 236 to 237 (dec.) elemental analysis as $C_{23}H_{25}NO_3 \cdot HCl$ C H N calculated(%) 69.08 6.55 3.50 found(%) 68.97 6.82 3.29
200		m.p.(°C): 195 to 196 elemental analysis as $C_{23}H_{27}NO \cdot HCl$ C H N calculated(%) 74.68 7.63 3.79 found(%) 74.72 7.77 3.78
201		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.10(13H,m), 2.60∿3.08(5H,m), 3.41(2H,S), 7.00∿7.85(4H,m), 7.19(5H,S). molecular formula: $C_{24}H_{29}NO \cdot HCl$
202		^{1}H-NMR($CDCl_3$) δ; 1.17(3H,d), 1.12∿2.10(9H,m), 2.60∿2.93(2H,m), 3.41(2H,S), 3.51(1H,q), 7.20(5H,S), 7.30∿7.92 (5H,m). molecular formula: $C_{22}H_{27}NO \cdot HCl$

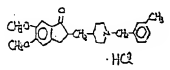
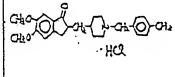
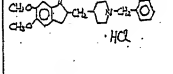
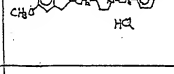
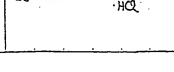
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
203		m.p.(°C): 126 to 127 elemental analysis as $C_{26}H_{33}NO_3 \cdot HCl$ C H N calculated(%) 70.33 7.72 3.15 found(%) 70.41 7.48 2.85
204		^{1}H-NMR($CDCl_3$) δ; 1.00∿3.40(20H,m), 3.50(2H,S), 3.90(3H,S), 3.97(3H,S), 6.88(1H,S), 7.18(1H,S), 7.31(5H,S). molecular formula: $C_{27}H_{35}NO_3 \cdot HCl$
205		^{1}H-NMR($CDCl_3$) δ; 1.05∿3.36(22H,m), 3.45(2H,S), 3.85(3H,S), 3.90(3H,S), 6.78(1H,S), 7.08(1H,S), 7.21(5H,S). molecular formula: $C_{28}H_{37}NO_3 \cdot HCl$
206		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.50(7H,m), 2.70∿3.02(2H,m), 3.48(2H,S), 3.56(2H,S), 3.79(3H,S), 6.69(1H,dt), 7.02∿7.50(3H,m), 7.21(5H,m). molecular formula: $C_{23}H_{25}NO_2 \cdot HCl$
207		^{1}H-NMR($CDCl_3$) δ; 1.50∿3.57(11H,m), 3.48, 3.50(total 2H, each S), 3.83, 3.85 (total 3H, each S), 6.57∿7.39(4H,m), 7.22(5H,m). molecular formula: $C_{23}H_{25}NO_2 \cdot HCl$

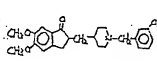
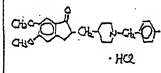
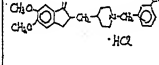
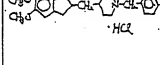
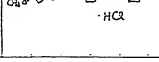
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
208		^{1}H-NMR($CDCl_3$) δ; 1.58∿2.55(7H,m), 2.79∿3.02(2H,m), 3.50(2H,S), 3.63(2H,d), 3.90 (6H,S), 6.63(1H,dt), 6.93(1H,d), 7.22(5H,S), 7.57(1H,d). molecular formula: $C_{24}H_{27}NO_3 \cdot HCl$
209		^{1}H-NMR($CDCl_3$) δ; 1.50∿2.55(7H,m), 2.78∿3.03(2H,m), 3.48(2H,S), 3.56(2H,d), 3.85(3H,S), 4.00(3H,S), 6.62(1H,dt), 7.07(1H,d), 7.21(1H,d), 7.22(5H,S). molecular formula: $C_{24}H_{27}NO_3 \cdot HCl$
210		^{1}H-NMR($CDCl_3$) δ; 1.50∿2.50(7H,m), 2.78∿3.03(2H,m), 3.48(2H,S), 3.53(2H,d), 3.82(3H,S), 3.90(3H,S), 4.03(3H,S), 6.58(1H,dt), 6.61(1H,S), 7.25(5H,S). molecular formula: $C_{25}H_{29}NO_4 \cdot HCl$
211		^{1}H-NMR($CDCl_3$) δ; 1.52∿2.55(7H,m), 2.78∿3.02(2H,m), 3.50(2H,S), 3.59(2H,S), 6.72(1H,dt), 7.05∿7.55(3H,m), 7.22(5H,S). molecular formula: $C_{22}H_{22}NOF \cdot HCl$
212		^{1}H-NMR($CDCl_3$) δ; 1.50∿2.55(7H,m), 2.38(3H,S), 2.78∿3.02(2H,m), 3.48(2H,S), 3.57(2H,S), 6.66(1H,dt), 7.38∿7.60 (3H,m), 7.21(5H,S). molecular formula: $C_{23}H_{25}NO \cdot HCl$

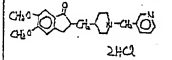
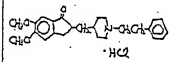
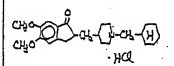
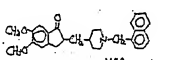
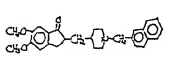
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
213		^{1}H-NMR($CDCl_3$) δ; 1.48∿2.60(7H,m), 2.32(3H,S), 2.77∿3.02(2H,m), 3,49(4H,S), 6.69(1H,dt), 7.10∿7.67(3H,m), 7.22(5H,S). molecular formula: $C_{23}H_{25}NO \cdot HCl$
214		m.p.(°C): 174 to 175 elemental analysis as $C_{23}H_{25}NO_3$ C H N calculated(%) 69.08 6.55 3.50 found(%) 69.12 6.41 3.43
215		m.p.(°C): 175 to 176 elemental analysis as $C_{30}H_{31}NO_3$ C H N calculated(%) 79.44 6.89 3.09 found(%) 79.04 6.87 2.77
216		m.p.(°C): 180 to 181 elemental analysis as $C_{26}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 70.65 7.30 3.17 found(%) 70.34 7.05 3.07
217		m.p.(°C): 228 to 230 (dec.) elemental analysis as $C_{23}H_{23}NO_3 \cdot HCl$ C H N calculated(%) 69.43 6.08 3.52 found(%) 67.89 5.97 3.45 1/2 H_2O (%) 67.89 6.19 3.44

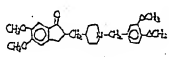
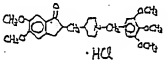
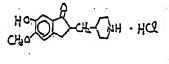
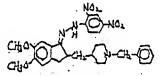
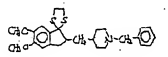
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
218		^{1}H-NMR($CDCl_3$) δ; 2.48∿3.02(13H,m), 3.48(2H,S), 6.73(1H,dt), 7.10∿8.10(4H,m), 7.22(5H,S). molecular formula: $C_{23}H_{25}NO \cdot HCl$
219		m.p.(°C): 211 to 213 (dec.) elemental analysis as $C_{24}H_{27}NO \cdot HCl$ C H N; calculated(%) 75.47 7.39 3.67; found(%) 75.22 7.41 3.57
220		^{1}H-NMR($CDCl_3$) δ; 1.20∿2.60(7H,m), 1.96(3H,d), 2.70∿2.97(2H,m), 3.46(3H,S), 6.67(1H,dd), 7.21(5H,S), 7.21∿7.61(5H,m). molecular formula: $C_{22}H_{25}NO \cdot HCl$
221		m.p.(°C): 170 to 171 elemental analysis as $C_{26}H_{31}NO_3$ C H N; calculated(%) 77.01 7.70 3.45; found(%) 77.10 7.67 3.43
222		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.40(13H,m), 2.70∿3.00(2H,m), 3.45(2H,S), 3.48(2H,S), 3.86(3H,S), 3.91(3H,S), 6.68(1H,tt), 6.80(1H,S), 7.20(6H,S). molecular formula: $C_{27}H_{33}NO_3 \cdot HCl$

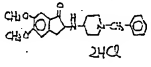
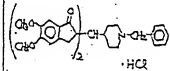
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
223		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.40(15H,m), 2.68∿3.00(2H,m), 3.46(2H,S), 3.50(2H,S), 3.88(3H,S), 3.93(3H,S), 6.68(1H,tt), 6.83(1H,S), 7.19(1H,S), 7.21(5H,S). molecular formula: $C_{28}H_{35}NO_3 \cdot HCl$
224		m.p.(°C): 130 to 135 elemental analysis as $C_{26}H_{29}NO_3 \cdot HCl$ C H N calculated(%) 70.98 6.87 3.18 found(%) 70.81 6.72 3.10
225		^{1}H-NMR($CDCl_3$) δ; 1.10∿3.50(16H,m), 3.87(3H,S), 3.93(3H,S), 6.80(1H,S), 7.00∿7.25 (6H,m). molecular formula: $C_{24}H_{29}NO_3 \cdot HCl$
226		m.p.(°C): 186 to 188 (dec.) ^{1}H-NMR($CDCl_3$) δ; 1.65∿2.10(7H,m), 2.65∿2.75(2H,m), 3.25∿3.83(5H,m), 3.92(3H,S), 3.98(3H,S), 4.60(2H,S), 6.88(1H,S), 7.19(1H,S), 7.26∿ 7.60(5H,m). molecular formula: $C_{24}H_{29}NO_4$
227		m.p.(°C): 220 to 221 elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 69.83 7.50 3.26 found(%) 70.03 7.51 3.26

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
228		m.p.(°C): 212 to 213 elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 69.83 7.50 3.26 found(%) 69.62 7.38 3.15
229		m.p.(°C): 229 to 230 (dec.) elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 69.83 7.50 3.26 found(%) 69.91 7.48 3.28
230		^{1}H-NMR($CDCl_3$) δ; 1.00∿3.50(14H,m), 3.73(2H,S), 3.86(3H,S), 3.93(3H,S), 6.82(1H,S), 7.12(1H,S), 7.22∿7.80(4H,m). molecular formula: $C_{24}H_{28}N_2O_5 \cdot HCl$
231		m.p.(°C): 210 to 211 elemental analysis as $C_{24}H_{28}N_2O_5 \cdot HCl$ C H N calculated(%) 62.54 6.34 6.08 found(%) 62.48 6.34 5.96
232		m.p.(°C): 234 to 236 (dec.) elemental analysis as $C_{24}H_{28}N_2O_5 \cdot HCl$ C H N calculated(5) 62.54 6.34 6.08 found(%) 62.56 6.25 5.83

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
233		^{1}H-NMR($CDCl_3$) δ; 1.10∿3.43(14H,m), 3.52(2H,S), 3.84(3H,S), 3.91(3H,S), 6.35∿7.08 (7H,m). molecular formula: $C_{24}H_{29}NO_4 \cdot HCl$
234		m.p.(°C): 146 to 148 elemental analysis as $C_{24}H_{29}NO_4 \cdot HCl$ C H N calculated(%) 66.51 7.29 3.53 found(%) 66.73 7.00 3.24
235		m.p.(°C): 193 to 194 elemental analysis as $C_{25}H_{31}NO_4 \cdot HCl$ C H N calculated(%) 67.33 7.23 3.14 found(%) 67.43 7.22 3.13
236		m.p.(°C): 226 to 228 (dec.) elemental analysis as $C_{25}H_{31}NO_4 \cdot HCl$ C H N calculated(%) 67.33 7.23 3.14 found(%) 67.21 7.29 2.97
237		^{1}H-NMR($CDCl_3$) δ; 0.78∿3.40(14H,m), 3.46(2H,S), 3.85(3H,S), 3.91(3H,S), 5.01(2H,S), 6.78(1H,S), 6.80∿7.43(9H,m), 7.09(1H,S). molecular formula: $C_{31}H_{35}NO_4 \cdot HCl$

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
238		m.p.(°C): 224 to 226 (dec.) elemental analysis as $C_{23}H_{28}N_2O_3 \cdot 2HCl$ C H N calculated(%) 60.93 6.67 6.18 found(%) 58.72 6.98 5.56 H_2O(%) 58.60 6.84 5.94
239		m.p.(°C): 253 to 256 (dec.) elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C H N calculated(5) 69.83 7.50 3.26 found(%) 69.60 7.49 3.27
240		m.p.(°C): 225 to 226 (dec.) elemental analysis as $C_{24}H_{35}NO_3 \cdot HCl$ C H O calculated(%) 68.31 8.60 3.32 found(%) 68.17 8.49 3.51
241		m.p.(°C): 226 to 227 (dec.) elemental analysis as $C_{28}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 72.17 6.92 3.01 found(%) 71.71 7.07 2.85
242		m.p.(°C): 243 to 245 (dec.) elemental analysis as $C_{28}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 72.17 6.92 3.01 found(%) 71.75 6.92 3.01

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
243		m.p.(°C): 191 to 192 elemental analysis as $C_{26}H_{33}NO_5 \cdot HCl$ C H N calculated(%) 65.60 7.20 2.94 found(%) 65.34 7.27 2.79
244		m.p.(°C): 219 to 221 elemental analysis as $C_{27}H_{35}NO_6 \cdot HCl$ C H N calculated(%) 64.09 7.17 2.77 found(%) 63.27 7.19 2.51 1/2 H_2O(%) 62.96 7.24 2.72
245		^{1}H-NMR(D_2O) δ; 1.10∿3.12(14H,m), 3.84(3H,S), 6.70(1H,S), 6.84(1H,S). molecular formula: $C_{16}H_{21}NO_3 \cdot HCl$
246		m.p.(°C): 182 to 183 elemental analysis as $C_{30}H_{33}N_5O_6$ C H N calculated(%) 64.39 5.94 12.51 found(%) 64.42 5.78 12.52
247		m.p.(°C): 240 to 241 (dec.) elemental analysis as $C_{26}H_{33}NO_2S_2 \cdot HCl$ C H N calculated(%) 63.46 6.96 2.85 found(%) 63.18 6.78 2.80

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
248		m.p.(°C): 180 to 185 (dec.) elemental analysis as $C_{23}H_{28}N_2O_3 \cdot 2HCl$ C: calculated(%) 60.73, found(%) 60.92 H: calculated(%) 6.45, found(%) 6.67 N: calculated(%) 6.25, found(%) 6.18
249		m.p.(°C): 230 to 232 (dec.) elemental analysis as $C_{35}H_{39}NO_6 \cdot HCl$ C: calculated(%) 69.35, found(%) 69.21 H: calculated(%) 6.65, found(%) 6.59 N: calculated(%) 2.31, found(%) 2.33

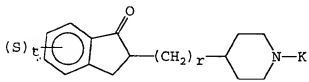
The compounds obtained in Examples 178 to 249 were each examined according to the above shown experimetal test in view of the inhibitory activity. Results are shown in Table 10.

Table 10

Inhibitory effect against acetylcholinesterase in vitro					
Compound	Inhibitory activity on AChE IC_{50}(μM)	Compound	Inhibitory activity on AChE IC_{50}(μM)	Compound	Inhibitory activity on AChE IC_{50}(μM)
178	>10	202	1.2	226	0.0049
179	5.4	203	0.009	227	0.01
180	0.001	204	0.035	228	0.002
181	0.094	205	0.014	229	0.04
182	0.8	206	0.41	230	0.16
183	5.3	207	0.049	231	0.004
184	>5	208	0.062	232	0.1
185	0.00082	209	0.43	233	0.046
186	0.0015	210	0.06	234	0.0018
187	4.4	211	2	235	0.22
188	0.081	212	0.5	236	3.6
189	0.012	213	0.05	237	2.6
190	0.02	214	0.0084	238	0.072
191	0.085	215	0.0042	239	0.18
192	0.013	216	0.017	240	0.0089
193	0.2	217	0.14	241	0.22
194	0.069	218	20	242	2.9
195	0.0071	219	19	243	4
196	0.0013	220	11	244	4.9
197	0.38	221	0.033	245	5
198	0.0054	222	0.011	246	4.4
199	0.023	223	0.0054	247	-
200	2.1	224	0.003	248	1.4
201	15	225	0.48	249	0.62

Claims

1. A process for preparing a cyclic amine compound of formula (I) or a pharmacologically acceptable salt thereof:



(I)

wherein:
S is a lower alkyl group having 1-6 carbon atoms, a lower alkoxy group having 1-6 carbon atoms, a halogen

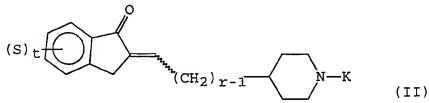
atom, a hydroxyl group, and t is 0-4, or $(S)_t$ may form a methylene dioxy group or an ethylene dioxy group on two adjacent carbon atoms of the phenyl group to which $(S)_t$ is attached;

r is an integer from 1 to 6; and

K is a phenylalkyl group optionally substituted by a C_{1-6} alkyl group which may optionally be halogenated, a C_{1-6} alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6} alkoxycarbonyl group, an amino group, a C_{1-6} monoalkylamino group, a C_{1-6} dialkylamino group, a carbamoyl group, a C_{1-6} acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6} alkoxy-C_{1-6} alkyl group;

comprising the steps of:

(i) reducing a cyclic amine of the formula (II)

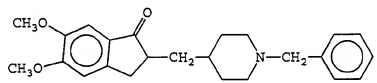


(II)

wherein S, t, r and K are as defined above; and

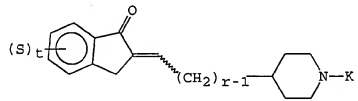
(ii) optionally converting the resulting compound of formula (I) into a pharmacologically acceptable salt.

2. A process according to Claim 1, wherein the compound of formula (I) is



or a pharmacologically acceptable salt thereof.

3. A process for preparing a cyclic amine compound of formula (II) or a pharmacologically acceptable salt thereof:

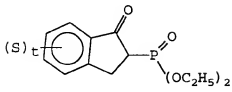


(II)

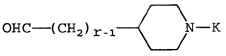
wherein S, t, r and K are as defined in Claim 1,

comprising the steps of:

(i) reacting in a Wittig reaction

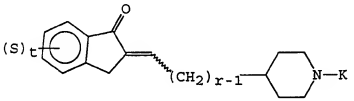


and



wherein S, t, r and K are as defined above; and
(ii) optionally converting the resulting compound of formula (II) into a pharmacologically acceptable salt.

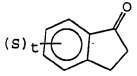
4. A process for preparing a cyclic amine compound of formula (II) or a pharmacologically acceptable salt thereof:



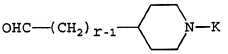
(II)

wherein S, t, r and K are as defined in Claim 1,
comprising the steps of:

(i) reacting:

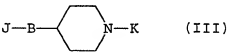


and



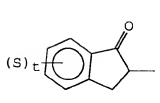
, wherein S, t, r and K are as defined above, in the presence of lithium diisopropylamide; and
(ii) optionally converting the resulting compound of formula (II) into a pharmacologically acceptable salt.

5. A process for preparing a cyclic amine compound of formula (III) or a pharmacologically acceptable salt thereof:



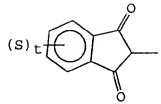
(III)

wherein:
K is as defined in Claim 1;
J is



indanonyl

or



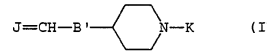
indanedionyl

wherein S and t are as defined in Claim 1; and

B is the divalent group $-(CHR^{22})_r-$, in which r is an integer from 1 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group;

comprising the steps of:

(i) reducing a cyclic amine of the formula (IV):



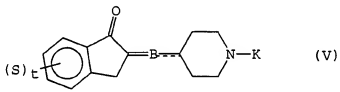
(IV)

wherein J and K are as defined above and B' corresponds to B but omitting the terminal group containing one carbon atom; and

(ii) optionally converting the resulting compound of formula (III) into a pharmacologically acceptable salt.

6. A process according to Claim 1 or Claim 5, wherein the reduction of step (i) is carried out catalytically.

7. A process for preparing a cyclic amine compound of formula (V) or a pharmacologically acceptable salt thereof:



(V)

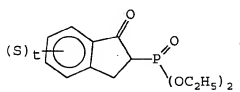
wherein S, t and K are as defined in Claim 1;

B is one of the divalent groups $=(CH\text{-}CH{=}CH)_b-$, in which b is an integer from 1 to 3; $=CH\text{-}(CH_2)_c-$ in which c is an integer from 0 to 9; or $=(CH\text{-}CH)_d=$, in which d is an integer from 0 to 5; and

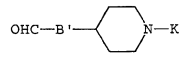
------ represents a single or a double bond,

comprising the steps of

(i) reacting in a Wittig reaction



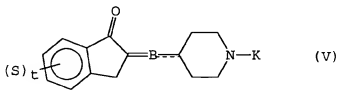
and



wherein S, t and K are as defined above and B' corresponds to B but omitting the terminal group containing one carbon atom; and

(ii) optionally converting the resulting compound of formula (V) into a pharmacologically acceptable salt.

8. A process for preparing a cyclic amine compound of formula (V) or a pharmacologically acceptable salt thereof:



(V)

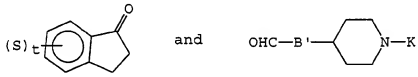
wherein S, t and K are as defined in Claim 1;

B is one of the divalent groups $=(CH\text{-}CH{=}CH)_b\text{-}$, in which b is an integer from 1 to 3; $=CH\text{-}(CH_2)_c\text{-}$, in which c is an integer from 0 to 9; or $=(CH\text{-}CH)_d=$, in which d is an integer from 0 to 5; and

------- represents a single or a double bond,

comprising the steps of

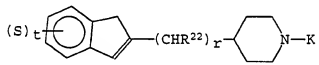
(i) reacting



wherein S, t and K is as defined above and B' corresponds to B but omitting the terminal group containing one carbon atom; and

(ii) optionally converting the resulting compound of formula (V) into a pharmacologically acceptable salt.

9. A process for preparing a cyclic amine compound of formula (VI) or a pharmacologically acceptable salt thereof:



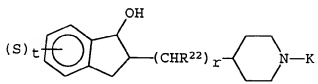
(VI)

wherein S, t and K are as defined in Claim 1; and

r is an integer from 0 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group;

comprising the steps of:

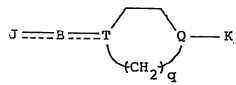
(i) dehydrating an indanol compound of formula



wherein S, t, r and K are as defined above; and

(ii) optionally converting the resulting compound of formula (VI) into a pharmacologically acceptable salt.

10. A cyclic amine compound having the following formula (XXV) and a pharmacologically acceptable salt thereof:



(XXV)

in which J is

(a) a group, substituted or unsubstituted, selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl and (7) furyl;
(b) a monovalent or divalent group, in which the phenyl may have a substituent(s), selected from the group consisting of (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl and (9) C_6H_5-CO-CH(CH_3)-;
(c) a monovalent group derived from a cyclic amide compound;
(d) a lower alkyl or
(e) a group of R^{21}-CH=CH- in which R^{21} is hydrogen or a lower alkoxycarbonyl;

B is -(CHR22)$_r$-, -CO-(CHR22)$_r$-, -NR^4-(CHR22)$_r$-, R^4 being hydrogen, a lower alkyl, an acyl, a lower alkylsulfonyl, phenyl, a substituted phenyl, benzyl or a substituted benzyl, -CO-NR^5-(CHR22)$_r$-, R^5 being hydrogen, a lower alkyl or phenyl, -CH=CH-(CHR22)$_r$-, -OCOO-(CHR22)$_r$-, -OOC-NH-(CHR22)$_r$-, -NH-CO-(CHR22)$_r$-, -CH_2-CO-NH-(CHR22)$_r$-, -(CH_2)$_2$-CO-NH-(CHR22)$_r$-, -CH(OH)-(CHR22)$_r$-, r being zero or an integer of 1 to 10, R22 being hydrogen or methyl so that one alkylene group may have no methyl branch or one or more methyl branch, =(CH-CH=CH)b-, b being an integer of 1 to 3, =CH-(CH_2)$_c$-, c being zero or an integer of 1 to 9, =(CH-CH)$_d$=, d being zero or an integer of 1 to 5; -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -CH(CH_3)-CO-NH-CH_2-, -CH=CH-CO-NH-(CH_2)$_2$-, -NH-, -O-, -S-, a dialkylaminoalkylcarbonyl or a lower alkoxycarbonyl;

T is nitrogen or carbon;
Q is nitrogen, carbon or >N→O; and
q is an integer of 1 to 3;
K is hydrogen, phenyl, a substituted phenyl, an arylalkyl in which the phenyl may have a substituent, cynnamyl, a lower alkyl, pyridylmethyl, a cycloalkylalkyl, adamantanemethyl, furylmethyl, a cycloalkyl, a lower alkoxycarbonyl or an acyl; and
---- shows a single bond or a double bond.

11. A cyclic amine compound as claimed in Claim 10 and a pharmacologically acceptable salt thereof, in which J is (a) or (b).

12. A cyclic amine compound as claimed in Claim 10 and a pharmacologically acceptable salt thereof, in which J is (b) selected from the group consisting of monovalent groups of (2), (3) and (5) and divalent groups of (2).

13. A cyclic amine compound as claimed in Claim 10 and a pharmacologically acceptable salt thereof, in which J is (b), (preferably (2) of (b)), and B is -(CHR22)r-, =(CH-CH=CH)b-, =CH-(CH2)c- or =(CH-CH)d=.

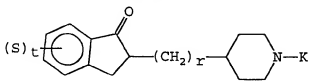
14. A cyclic amine compound as claimed in Claim 13 and a pharmacologically acceptable salt thereof, in which Q is nitrogen, T is carbon or nitrogen and n is 2; Q is nitrogen, T is carbon and n is 1 or 3; or Q is carbon, T is nitrogen and n is 2.

15. A cyclic amine compound as claimed in Claim 10 and a pharmacologically acceptable salt thereof, in which Q is nitrogen, T is carbon and n is 2.

16. A cyclic amine compound as claimed in Claim 14 and a pharmacologically acceptable salt thereof, in which K is a phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

Claims for the following Contracting State : GR

1. A process for preparing a cyclic amine compound of formula (I) or a pharmacologically acceptable salt thereof:



(I)

wherein:

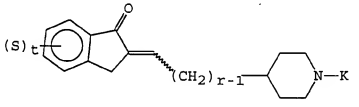
S is a lower alkyl group having 1-6 carbon atoms, a lower alkoxy group having 1-6 carbon atoms, a halogen atom, a hydroxyl group, and t is 0-4, or $(S)_t$ may form a methylene dioxy group or an ethylene dioxy group on two adjacent carbon atoms of the phenyl group to which $(S)_t$ is attached;

r is an integer from 1 to 6; and

K is a phenylalkyl group optionally substituted by a C_{1-6} alkyl group which may optionally be halogenated, a C_{1-6} alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6} alkoxycarbonyl group, an amino group, a C_{1-6} monoalkylamino group, a C_{1-6} dialkylamino group, a carbamoyl group, a C_{1-6} acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6} alkoxy-C_{1-6} alkyl group;

comprising the steps of:

(i) reducing a cyclic amine of the formula (II)

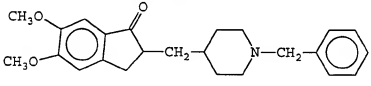


(II)

wherein S, t, r and K are as defined above; and

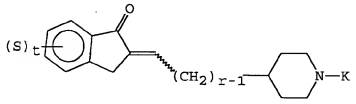
(ii) optionally converting the resulting compound of formula (I) into a pharmacologically acceptable salt.

2. A process according to Claim 1, wherein the compound of formula (I) is



or a pharmacologically acceptable salt thereof.

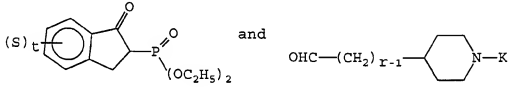
3. A process for preparing a cyclic amine compound of formula (II) or a pharmacologically acceptable salt thereof:



(II)

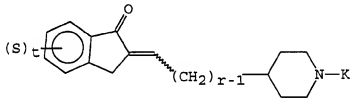
wherein S, t, r and K are as defined in Claim 1,
comprising the steps of:

(i) reacting in a Wittig reaction



wherein S, t, r and K are as defined above; and
(ii) optionally converting the resulting compound of formula (II) into a pharmacologically acceptable salt.

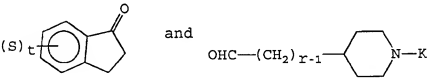
4. A process for preparing a cyclic amine compound of formula (II) or a pharmacologically acceptable salt thereof:



(II)

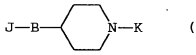
wherein S, t, r and K are as defined in Claim 1,
comprising the steps of:

(i) reacting:



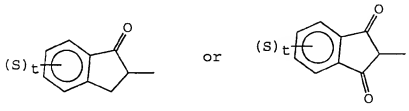
, wherein S, t, r and K are as defined above, in the presence of lithium diisopropylamide; and
(ii) optionally converting the resulting compound of formula (II) into a pharmacologically acceptable salt.

5. A process for preparing a cyclic amine compound of formula (III) or a pharmacologically acceptable salt thereof:



(III)

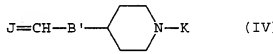
wherein: K is as defined in Claim 1;
J is



indanonyl or indanedionyl

wherein S and t are as defined in Claim 1; and
B is the divalent group $-(CHR^{22})_r-$, in which r is an integer from 1 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group;
comprising the steps of:

(i) reducing a cyclic amine of the formula (IV):

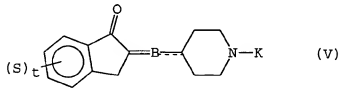


(IV)

wherein J and K are as defined above and B' corresponds to B but omitting the terminal group containing one carbon atom; and
(ii) optionally converting the resulting compound of formula (III) into a pharmacologically acceptable salt.

6. A process according to Claim 1 or Claim 5, wherein the reduction of step (i) is carried out catalytically.

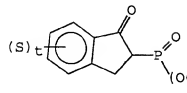
7. A process for preparing a cyclic amine compound of formula (V) or a pharmacologically acceptable salt thereof:



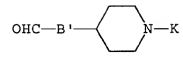
(V)

wherein S, t and K are as defined in Claim 1;
B is one of the divalent groups $=(CH\text{-}CH{=}CH)_b-$, in which b is an integer from 1 to 3; $=CH\text{-}(CH_2)_c-$ in which c is an integer from 0 to 9; or $=(CH\text{-}CH)_d=$, in which d is an integer from 0 to 5; and
------- represents a single or a double bond,
comprising the steps of

(i) reacting in a Wittig reaction



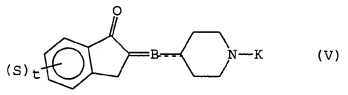
and



wherein S, t and K are as defined above and B' corresponds to B but omitting the terminal group containing one carbon atom; and

(ii) optionally converting the resulting compound of formula (V) into a pharmacologically acceptable salt.

8. A process for preparing a cyclic amine compound of formula (V) or a pharmacologically acceptable salt thereof:

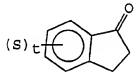


wherein S, t and K are as defined in Claim 1; B is one of the divalent groups $=(CH\text{-}CH{=}CH)_b\text{-}$, in which b is an integer from 1 to 3; $=CH\text{-}(CH_2)_c\text{-}$, in which c is an integer from 0 to 9; or $=(CH\text{-}CH)_d=$, in which d is an integer from 0 to 5; and

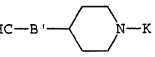
------ represents a single or a double bond,

comprising the steps of

(i) reacting



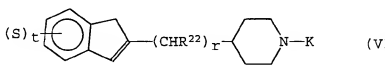
and



wherein S, t and K is as defined above and B' corresponds to B but omitting the terminal group containing one carbon atom; and

(ii) optionally converting the resulting compound of formula (V) into a pharmacologically acceptable salt.

9. A process for preparing a cyclic amine compound of formula (VI) or a pharmacologically acceptable salt thereof:

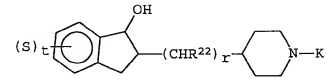


wherein S, t, and K are as defined in Claim 1; and

r is an integer from 0 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group;

comprising the steps of:

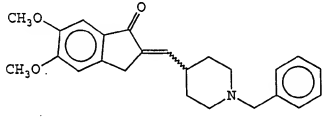
(i) dehydrating an indanol compound of formula



wherein S, t, r and K are as defined above; and

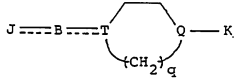
(ii) optionally converting the resulting compound of formula (VI) into a pharmacologically acceptable salt.

10. A synthetic intermediate compound of the structural formula:



no claim being made to this compound as a pharmaceutical.

11. A cyclic amine compounds having the following formula (XXV) and a pharmacologically acceptable salt thereof:



(XXV)

in which J is

(a) a group, substituted or unsubstituted, selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl may have a substituent(s), selected from the group consisting of (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl and (9) C_6H_5-CO-CH(CH_3)-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl or

(e) a group of R^{21}-CH=CH- in which R^{21} is hydrogen or a lower alkoxycarbonyl;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, R^4 being hydrogen, a lower alkyl, an acyl, a lower alkylsulfonyl, phenyl, a substituted phenyl, benzyl or a substituted benzyl, -CO-NR^5-$(CHR^{22})_r$-, R^5 being hydrogen, a lower alkyl or phenyl, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, -CH_2-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-CO-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, r being zero or an integer of 1 to 10, R22 being hydrogen or methyl so that one alkylene group may have no methyl branch or one or more methyl branch, =(CH-CH=CH)b-, b being an integer of 1 to 3, =CH-$(CH_2)_c$-, c being zero or an integer of 1 to 9, =(CH-$CH)_d$=, d being zero or an integer of 1 to 5; -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -CH(CH_3)-CO-NH-CH_2-, -CH=CH-CO-NH-$(CH_2)_2$-, -NH-, -O-, -S-, a dialkylaminoalkylcarbonyl or a lower alkoxycarbonyl;

T is nitrogen or carbon;

Q is nitrogen, carbon or >N→O; and

q is an integer of 1 to 3;

K is hydrogen, phenyl, a substituted phenyl, an arylalkyl in which the phenyl may have a substituent, cynnamyl, a lower alkyl, pyridylmethyl, a cycloalkylalkyl, adamantanemethyl, furylmethyl, a cycloalkyl, a lower alkoxycarbonyl or an acyl; and

---- shows a single bond or a double bond.

12. A cyclic amine compound as claimed in Claim 11 and a pharmacologically acceptable salt thereof, in which J is (a) or (b).

13. A cyclic amine compound as claimed in Claim 11 and a pharmacologically acceptable salt thereof, in which J is (b) selected from the group consisting of monovalent groups of (2), (3) and (5) and divalent groups of (2).

14. A cyclic amine compound as claimed in Claim 11 and a pharmacologically acceptable salt thereof, in which J is (b), (preferably (2) of (b)), and B is -(CHR22)r-, =(CH-CH=CH)b-, =CH-(CH2)c- or =(CH-CH)d=.

15. A cyclic amine compound as claimed in Claim 14 and a pharmacologically acceptable salt thereof, in which Q is nitrogen, T is carbon or nitrogen and n is 2; Q is nitrogen, T is carbon and n is 1 or 3; or Q is carbon, T is nitrogen and n is 2.

16. A cyclic amine compound as claimed in Claim 11 and a pharmacologically acceptable salt thereof, in which Q is nitrogen, T is carbon and n is 2.

17. A cyclic amine compound as claimed in Claim 15 and a pharmacologically acceptable salt thereof, in which K is a phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 96 11 0252

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 042 322 (PHARMINDUSTRIE) 23 December 1981 see RN 81270-51-1, 1H-Inden-1-one, 2,3-dihydro-2-[3-[1-(triphenylmethyl)-4-piperidinyl]propyl]- see RN 81270-46-4, 1H-Inden-1-one, 2,3-dihydro-2-(4-piperidinylmethyl)-, hydrochloride see RN 81270-45-3, 1H-Inden-1-one, 2,3-dihydro-2-(4-piperidinylmethyl)- --- -/--	10-15	C07D211/22 C07D211/26 C07D211/76 C07D211/34 C07D207/09 C07D401/06 C07D401/12 C07D405/12 A61K31/445

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	3 September 1996	Kissler, B

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 0252

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	INDIAN J. CHEM., SECT. B, vol. 15B, no. 7, 1977, pages 641-644, XP002012183 GUPTA, R. C. ET. AL.: "3-Aminoacrylophenones and some related compounds: a new class of anti-inflammatory agents" see RN 65201-48-1, 1H-Inden-1-one, 4-chloro-2,3-dihydro-2-[[4-(2-methoxyphenyl)-1- piperazinyl]methylene]- see for example RN 65201-47-0, 1H-Inden-1-one, 6-fluoro-2,3-dihydro-2-[[4-(4-methoxyphenyl)-1- piperazinyl]methylene]- ---	10-15	
X	US-A-4 130 646 (B. RICHARD VOGT; DAVID A. CULLISON) 19 December 1978 see for example RN 62811-29-4, 1H-Inden-1-one, 2,3-dihydro-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-, monohydrochloride see for example RN 62811-26-1, 1H-Inden-1-one, 2,3-dihydro-5,6-dimethoxy-2-[[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]methyl]- --- -/--	10-14	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 0252

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DE-A-20 21 262 (CASSELLA) 11 November 1971 see for example RN 34924-83-9, 1H-Inden-1-one, 4-chloro-2,3-dihydro-2-[(4-phenyl-1-piperazinyl)methylene]- see for example RN 34924-79-3, 1H-Inden-1-one, 2-[(4-butyl-1-piperazinyl)methylene]-2,3-dihydro- see for example RN 34924-77-1, 1-Piperazinecarboxylic acid, 4-[(4-chloro-1,3-dihydro-1-oxo-2H-inden-2-ylidene)methyl]-, butyl ester ---	10-14	
X	US-A-3 454 565 (SIDNEY ROBERT SAFIR; RICHARD PRESTON WILLIAMS) 8 July 1969 see for eaxmple RN 23780-21-4, 1-Indanone, 5,6,7-trimethoxy-2-[(4-methyl-1-piperazinyl)methylene]- ---	10-14	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
P,X	EP-A-0 229 391 (EISAI) 22 July 1987 * the whole document * ---	10-16	
X	DE-A-26 33 214 (SQUIBB) 17 February 1977 Formulae I and IV of claims 1 and 20 and corresponding examples ---	10-15	
A	EP-A-0 207 913 (ASTRA) 7 January 1987 * the whole document * ---	10-16	
X	EP-A-0 112 776 (RHONE-POULENC) 4 July 1984 * claim 1 * formula VI on page 9, and examples; e.g. ex. 49,50 --- -/--	10,11, 14-16	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 0252

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 101, no. 17, 22 October 1984 Columbus, Ohio, US; abstract no. 151875, XP002012184 structure II & JP-A-59 076 082 (KYOWA HAKKO KOGYO CO.) 28 April 1984 ---	10,11, 14,15	
X	J. ORG. CHEM., vol. 38, no. 17, 24 August 1973, pages 3004-3011, XP000578329 R. L. AUGUSTINE ET. AL.: "Sythesis of .alpha.-Monosubstituted Indoles" * table II * ---	10,11, 14-16	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X,P	EP-A-0 236 263 (CIBA-GEIGY) 9 September 1987 * claim 1 * * page 3, line 7 - line 11 * ---	10,14	
X	CHEMICAL ABSTRACTS, vol. 102, no. 11, 18 March 1985 Columbus, Ohio, US; abstract no. 95509, XP002012185 formula III & ARCHIV. PHARM., vol. 317, no. 12, 1984, pages 1010-1017, ---	10,11, 14-16	
X	US-A-4 254 127 (J. VANDENBERK ET. AL.) 3 March 1981 see intermediates, col. 17-23; e.g. ex. XII -----	10,11, 14-16	

EPO FORM 1503 03.82 (P04C16)

European Patent Office EP 96110252 - C -

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extend that is not possible to carry out a meaningfull search info state of the art on the basis of some of the claims.

Claims searched completely: 1-9
Claims searched incompletely: 10-16
Claims not searched:

Reason for the limitation of the search:

The generic formula I contains almost no fixed structural moiety. In addition, the large number of values for most of the variables, in conjunction with their cascading meanings, renders the scope of the invention for which protection is sought ill-defined and obscure. Consequently, a complete search is precluded for practical and economic reasons.

Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

Compounds and processes for their preparation of:

4-(1-H-Inden-1-one-2,3-dihydro)-,4-(1-H-Inden-1,3-dione-2,3-dihydro)-,4-(1-H-Inden-2-yl)-alkyl/alkenyl-N-phenylalkylpiperidines

(Cf. Arts. 83,84 EPC, Rule 45 EPC, Guidelines Exam. Part B, Chapt. III, 3.6,3.7)